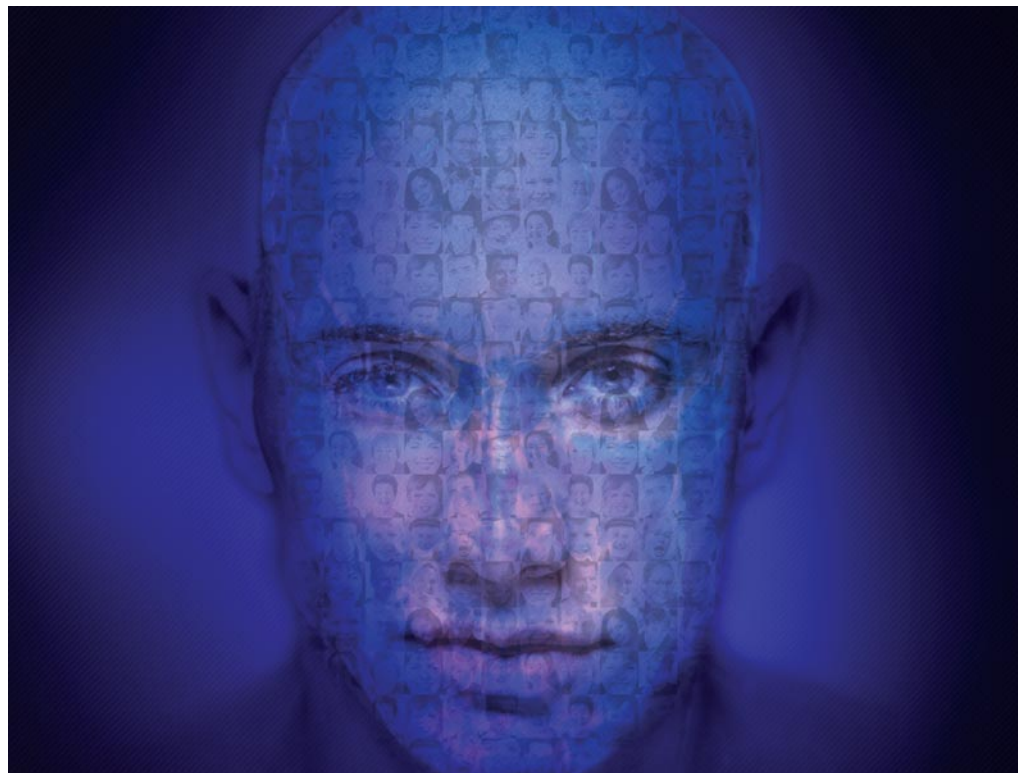


## Facial transplantation: where it is now and its future in reconstructive surgery



### Abstract

Facial transplantation has emerged in recent years as a promising treatment option for patients with severe facial disfigurement and is of wider interest to the lay community. In its short history, many technical, ethical and management challenges have been overcome. Over 15 transplants have been performed across the world for traumatic injuries, burns and congenital defects, with good functional and aesthetic outcomes being reported from cases. Significant issues involving the procedure persist, including the use of appropriate immunosuppressive regimes, statistics on long-term outcomes and patient selection processes. Patient selection is perhaps the most important factor in the success of the procedure, as the individual must endure difficult rehabilitative, psychological and social issues in the postoperative recovery period, including the adverse effects and complications associated with immunosuppression. Knowledge about long-term outcomes is still limited, with the first operation having only been performed in 2005. Follow-up and prospective studies are required before facial transplantation can become a widely offered treatment. Current progress in addressing these therapeutic issues suggests that it should not be long before facial transplantation becomes a realistic treatment option for a wide range of patients suffering from facial disfigurement, offering them an improved quality of life and the chance to successfully reintegrate into society.

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*FIGURE 1: Photographs showing the change undergone by three patients who had full facial transplantation surgery under Dr Bohdan Pomahac in Brigham and Women's Hospital, Boston, Massachusetts. Photographs were taken before and after the procedure and during recovery at four months (patient 1), three months (patient 2) and two months (patient 3). Even at this early stage, patients 1 and 2 regained some basic motor functions, including smiling and pouting.*

## Introduction

In recent years, reconstructive surgeons have been able to offer an increasing array of procedures to repair severe disfigurements with considerable success. The most recent developments have occurred in the field of facial transplantation using composite tissue allografts (CTAs). As a fledgling specialty within the field of reconstructive surgery, these operations are facing considerable scrutiny regarding their justification from a medical, ethical and societal perspective. Furthermore, while undoubtedly requiring immensely creative and skilled surgical technique, facial allograft transplantation (FAT) operations present the whole multidisciplinary team with novel patient management challenges, and development of best practice in this area is ongoing.<sup>1</sup> Concerns surrounding this operation include whether patients can cope with lifelong immunosuppression and the psychological, social, media and rehabilitative issues that arise in the course of their management.<sup>2</sup>

Another important consideration is the utility of developing this pioneering procedure. It could be argued that FAT exists simply

as a display of the extent of surgical capability rather than as a valid long-term strategy for reconstruction. However, traditional options – including skin grafts, flaps and prosthetics – have so far failed to provide adequate functional or aesthetic outcomes for patients.<sup>3</sup> One study reviewed 1,193 cases where maxillofacial prostheses were used to cover patients' severe facial disfigurements, many of whom may have seen better outcomes from partial facial transplantation.<sup>4</sup> While appropriate patient selection and donor-recipient matching limit the number of procedures being performed, the indications for facial transplantation currently include traumatic injury,<sup>5,6</sup> burns,<sup>7</sup> congenital defects,<sup>8</sup> malignant disease<sup>3</sup> and possibly even infectious diseases or significant minor defects.<sup>9</sup> Although there are many barriers to be overcome, FAT may present an alternative to maxillofacial prosthesis and surgical grafts and flaps in the treatment of severe facial disfigurement, and may indeed be a superior therapy. This review will discuss the status quo and future challenges in the field of facial transplantation.

**Table 1: Details on some of the facial transplantation procedures performed over recent years.**

Year	Indication	Extent of transplanted tissue	Current outcome status
2005 <sup>5</sup>	Trauma	Partial	Good functional and aesthetic outcome, particularly sensory function
2006 <sup>6</sup>	Trauma	Partial	Patient died after cessation of immunosuppressive therapy <sup>11</sup>
2007 <sup>8</sup>	Neurofibromatosis	Almost full	Good functional and aesthetic outcome, excellent quality of life improvement
2008 <sup>12</sup>	Trauma	Partial face and maxilla	Good functional and aesthetic outcome
2008 <sup>13</sup>	Neurofibromatosis	Partial	Large blood loss during surgery, but good outcome to date
2009 <sup>14</sup>	Trauma	Partial face, maxilla and mandible	Particularly good motor function recovery, improvement in quality of life and re-employment
2009 <sup>14</sup>	Burn	Combined partial face and bilateral hand	Patient died of cardiac arrest during second surgery for the treatment of a facial infection developed two months after transplantation
2009 <sup>14</sup>	Trauma	Partial face, maxilla and mandible	Improvement in quality of life and return to employment, but slower recovery of sensory and motor function
2009 <sup>15</sup>	Burn	Partial	Good functional and aesthetic outcome
2010 <sup>16</sup>	Trauma	Full	Too early to comment on outcome
2010 <sup>17</sup>	Neurofibromatosis	Full, including lacrimal ducts and lips	Too early to comment on outcome
2011 <sup>18</sup>	Burn	Full	Too early to comment on outcome; patient is blind, so motor and sensory recovery may be impaired

## Facial transplantation: history and present situation

Since the first FAT was performed in 2005 in Amiens, at least 18 FATs have been undertaken, not all of which have been reported in the literature as yet.<sup>10</sup> Each procedure has been unique in terms of indication, extent of transplanted tissue and outcomes (Table 1).<sup>5,6,8,12-18</sup> Most transplantations have involved more than one functional and aesthetic unit of the face, with all patients thus far having more than a 25% pre-operative facial disfigurement. The extent of tissue transferred has varied in each, ranging from simply skin, fat and muscle to bone, bone marrow, mucosa, cartilage and glandular, lymphatic, nervous or vascular tissue, and the consequent antigenic exposure levels.<sup>19</sup> Currently, no classification system exists to define the extent of facial transplantation.

Akin to free flap surgeries, the procedures invariably involve the microsurgical connection of donor graft vessels to recipient vasculature, and most have also involved various degrees of motor and sensory neuroorrhaphy. Some have also involved bone and cartilage transfer, which requires extra dissection and

fixation.<sup>20</sup> Blood loss is usually substantial and most of the operations take between 15 and 24 hours to complete with several surgical and anaesthetic specialists working in tandem.<sup>9</sup> Further surgery may be required at a later stage for debulking, aesthetic remodelling or the management of any complications that may arise.<sup>7</sup>

There are a small number of programmes in France, Spain, the United States, China and the UK – where the team leader is Professor Peter Butler, an RCSI graduate and fellow<sup>21</sup> – that have received clearance for facial transplantation by their respective governing bodies. Long-term data on procedures performed at these centres are awaited.

## Medical, psychosocial and ethical considerations

### Rehabilitation

The recovery process following the completion of the surgery is intensive. Early, aggressive rehabilitation is implemented with co-ordinated effort from specialist nursing, physiotherapy, speech and language therapy, nutritional care and the medical

team. Significant nerve regeneration must occur to recover full motor and sensory function, and the process can take a long time. Normal sensory abilities require roughly six months for recovery, and taste and smell sensation can also be re-established.<sup>12</sup> Motor functions that can be regained include mastication, swallowing, speaking and facial expression, but these require a longer recovery time and may depend on an intact sensory system to co-ordinate fine movement. Tacrolimus, an agent used in the immunosuppressive regimen, has also been shown to facilitate nerve regeneration.<sup>22</sup>

### Immunosuppression and the risk of rejection

The immunosuppressive regimen for post-transplantation patients is rigorous, and it is difficult to balance the potential for graft rejection against toxic effects and opportunistic infections.<sup>23</sup> Patients undergoing FAT tend to be younger than other transplant recipients, and thus the cumulative effects of long-term immunosuppression could exert a greater effect. As with all transplantation, side-effects are common; continuous prophylaxis against opportunistic infection and skilled professional monitoring for signs of rejection are required. These tasks must be performed diligently, as it is more difficult to replace a failing FAT than to replace, for example, a failing renal transplant. Rejection leading to the loss of a transplant may lead to a worse result than the original disfigurement, as the removal of the graft may be required. Currently, the longevity of transplanted facial tissue is unknown, although results from early CTAs are promising. Notably, two patients who have received FATs have since died (Table 1). One patient in China died after alternative medicine practitioners advised him to discontinue immunosuppressive therapy, and another patient in France died during a second surgery intended to treat a graft infection. Despite these unfortunate setbacks, it should be noted that the cause of death in both cases was not directly due to the FAT procedure, but rather as a result of problems faced during the postoperative management of the patient.

### Psychosocial issues and the ethics of identity transfer

With the demands of the therapeutic regimen and intensive rehabilitation, psychological resilience is a significant prerequisite for patients. As such, any social considerations or mental and/or physical co-morbidities must be identified and optimally managed before the transplantation is performed. Thorough and robust psychological assessment is essential and possible tools are in development, guided by those used in solid organ transplantation.<sup>24</sup> The patient's social situation, family support and religious beliefs are important factors in their re-integration into society. Highly skilled care in the community and continuous social work support are required. Aesthetics are another key patient concern. Donor matching along the lines of skin tone, skin volume, gender and facial skeletal units is required. The patient should be reminded that

the optimal aesthetic outcome may take years to develop and further surgical revisions may be necessary. Inevitably, media interest in these procedures is high, and concern of donor recognition has thus been sensationalised.<sup>2</sup>

A major ethical quandary surrounding facial transplantation is the issue of identity transfer.

There has been much public debate on the issue.<sup>18</sup> Concerns regarding identity transfer are countered by proponents of the procedure, who argue that neither the donor nor the recipient's identity is intact after the completion of a facial transplantation, but rather a 'third' face is created, which the recipient will come to recognise as his/her own once functional recovery has been achieved and uniquely personal facial movements can be performed.<sup>25</sup> Moreover, the recipient's original identity cannot be recovered due to the original disfigurement that provided the indication for reconstructive surgery.

Despite these concerns from some, the procedure does seem to be publicly acceptable; 90% of people were in favour of the principle of FAT in a public engagement exercise and the main barriers were perceived as technical rather than concerning issues of identity, albeit that the sample population was from the scientific community.<sup>26</sup> Patients can also be reassured when it comes to recognition after facial transplantation. A computer simulation study was used to create images with 'transplantation' of faces and participants were able to recognise the original face in 66% of cases and donor appearance in only 2.6%.<sup>27</sup>

### Informed consent

Full, independent and objective disclosure of the known risks and benefits of a therapy and clear patient understanding are essential to ensure autonomy of decision.<sup>2</sup>

In the case of FATs, an emphasis must be placed on psychological aspects, as the identity issues and rigorous post-operative management one encounters can be a source of significant stress.

There is worry that the social pressure of aesthetics may mitigate true voluntariness and that distress may compromise capacity. In terms of social pressure, it should be emphasised to the potential recipient that FAT primarily aims to restore normality and functionality rather than enhancing aesthetics. As for patient distress, the surgery itself will be correcting the source of distress and so the patient's decision-making should be approached in the same way as any other ameliorative surgery and does not interfere with capacity.

### Utility of facial transplantation

Justification of the procedure is a complex ethical argument, but is fundamentally a risk–benefit and cost–benefit assessment. Lifelong immunosuppression is necessary for the treatment of what is a non-life-threatening condition, and may actually shorten the patient's life expectancy. Moreover, although improvements in surgical technique have made the long-term

outcome of CTAs acceptable, there remains a risk of graft failure.<sup>28</sup> However, in the context of unsatisfactory traditional reconstructive alternatives, the patient may deem the complications of the procedure an acceptable risk that is outweighed by the benefit of an improved quality of life.<sup>7</sup> Ultimately, it will be up to the patient to determine if their current situation is grave enough for them to want the procedure while, conversely, there should be clear indications set out by the health boards and proposals exist for this.<sup>29</sup> Given the limited amount of literature on the subject, rigorous cost–benefit analysis cannot be conducted on FAT and current data is purely theoretical. Best estimates suggest that the costs of facial transplantation may equal those of heart transplantation, plus the cost of lifelong immunosuppression.<sup>30</sup> The value for such a figure may be found in the potential for productive living through the reintroduction of the patient into social and occupational life following FAT. Moreover, one may argue that the costs of the multiple procedures in traditional major facial reconstruction, in addition to the stigmatisation and withdrawal of patients from society, would be equal if not greater.

### Current challenges to FAT Immunosuppression

Adverse outcomes due to immunosuppression continue to be the principal limiting factors in facial transplantation,<sup>9</sup> although there is ongoing research into regimens that are associated with lower morbidity – for example tacrolimus monotherapy maintenance.<sup>31</sup>

Present evidence suggests that the antigenic load in CTAs does not generate as considerable an immune response as was once suspected, so reduced-dose regimens or better targeted agents may be effective here.<sup>32</sup>

### Long-term outcomes

As of 2011, outcomes of FAT are limited to six years and the sample size is very limited. While there have been episodes of acute rejection, in which the grafts respond well to treatment, there is little currently known about chronic rejection. Favourable comparisons can be made to solid organ transplants and better-than-expected outcome results have been achieved in many cases, but long-term data and knowledge about best rehabilitative processes are awaited.<sup>9</sup>

### Patient selection

Suitability for receiving the transplant will continue to be a challenge to the widespread use of FAT. With optimal rehabilitative, psychosocial and pharmacological management guidelines being developed, the range of indications for FAT may expand. There need not be barriers if fully informed consent is provided, but it is important not to be too zealous and alternative treatments associated with lower morbidities should be discussed with the patient before introducing the possibility of FAT.<sup>33</sup>

### Financial considerations

As with most transplant surgery, the costs involved in FAT pose a challenge, particularly since the patients that require lifelong immunosuppression are, on average, younger than other transplant patients. The costs involved in postoperative management and continuing care should be the biggest target in ensuring cost–benefit justification, although robust cost–benefit analysis cannot be completed until more long-term data become available.

### Classification

A classification system that distinguishes prognostic factors, outcome goals and potential immunosuppressant regimens could inform the standardised management of FAT patients. A triple system, which takes into account anatomical/aesthetic facial compartments, level of antigenic exposure and sensorimotor functional units, could be employed.

### Alternative treatment options

As the field of FAT continues to evolve, research is also being undertaken into alternative options. In the future, precise autologous tissue engineering,<sup>34</sup> better facial prostheses or significant improvements on traditional methods may offer outcomes that negate the need for FAT and reduce patient morbidity. However, current trends demonstrate that autologous tissue engineering is still a long way from widespread therapeutic use, and that FAT outperforms traditional methods or prostheses in functionality and aesthetic outcome.

### Concomitant CTAs

Often, incidents that have caused damage to the face, such as burns or trauma, also damage the hands, as they are used reactively to shield the face from injury. The first face and bilateral hand transplant was performed in France, but the patient died and the procedure carries serious risks. It is a great technical challenge to both surgeons and anaesthetists intra-operatively and a greater challenge to the patient with rehabilitation. There is also an increased potential for rejection due to a higher antigenic load. However, the development of successful concomitant CTAs could lead to severely incapacitated patients receiving various cadaveric body parts in just one operation. Research in both animals and humans suggests that these procedures may soon become viable.<sup>35</sup>

### Conclusion

Facial transplantation is becoming a realistic therapeutic option for patients suffering from severe facial disfigurements. Advances in CTA transplantation and immunosuppressive therapy have led to the technical feasibility of FAT across a range of indications from traumatic injuries to burns and congenital conditions. The current state of the field suggests



that it could become a mainstream addition to the reconstructive ladder, albeit a specialised procedure reserved for patients who satisfy stringent selection criteria. There are strong arguments that suggest an ethical justification for the procedure, but restrictions must be imposed such that only multidisciplinary teams that have appropriate skill and experience to deliver a high standard of care are allowed to manage these patients. Future research should focus on long-term medical and psychosocial outcomes of

post-transplant patients. In addition, studies should strive to identify the least morbid immunosuppressive regimen, so that evidence-based medicine, rather than correlations to other transplant procedures, informs clinical guidelines. Facial transplantation is an exciting and developing aspect of reconstructive surgery, which offers severely disfigured patients a chance to regain their humanity and dignity, both physically and socially. Facial allograft transplantation will become a valuable tool in the armoury of reconstructive surgeons.

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