Craniofacial Measurements of Donors and Recipients Correlate with Aesthetic Outcome in Virtual Face Transplantation

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Background: Face transplantation is an increasingly feasible option for patients with severe disfigurement. Donors and recipients are currently matched based on immune compatibility, skin characteristics, age, and gender. Aesthetic outcomes of the match are not always optimal and not possible to study in actual cases due to ethical and logistical challenges. We have used a reproducible and inexpensive three-dimensional virtual face transplantation (VFT) model to study this issue.
Methods: Sixty-one VFTs were performed using reconstructed high-resolution computed tomography angiographs of male and female subjects aged 20–69 years. Twenty independent reviewers evaluated the level of disfigurement of the posttransplant models. Absolute differences in 9 soft-tissue measurements and 16 bony cephalometric measurements from each of the VFT donor and recipient pretransplant model pairs were correlated to the reviewers' evaluation of disfigurement after VFT through a multivariate logistic regression model.
Results: Five soft-tissue measurements and 3 bony measurements were predictive of the rating of disfigurement after VFT (odds ratio; 95% confidence interval): trichion-to-nasion facial height (1.106; 1.066–1.148), endocanthal width (1.096; 1.051–1.142), exocanthal width (1.067; 1.036–1.099), mouth/chelion width (1.064; 1.019–1.110), subnasale-to-menton facial height (1.029; 1.003–1.056), inner orbit width (1.039; 1.009–1.069), palatal plane/occlusal plane angle (1.148; 1.047–1.258), and sella-nasion/mandibular plane angle (1.079; 1.013–1.150).
Conclusions: This study provides early evidence for the importance of soft-tissue and bony measurements in planning of facial transplantation. With future improvements to immunosuppressive regimens and increased donor availability, these measurements may be used as an additional criterion to optimize posttransplant outcomes. *(Plast Reconstr Surg Glob Open 2015;3:e385; doi: 10.1097/GOX.0000000000000343; Published online 1 May 2015.)*

Face transplantation is an increasingly feasible treatment option for patients with severe disfigurement. The first human face transplantation was performed less than a decade ago in France,[1] and since then, more than 25 interventions have followed across the world.[2–9] The advantages of face transplantation over conventional reconstruction are in its ability to provide superior aesthetic

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and functional outcomes with a single operation and without morbidity of multiple donor sites. These advantages are possible because face transplantation replaces "like-with-like" (ie, it transplants donated anatomical equivalents of the damaged facial parts), as opposed to conventional reconstruction which uses autologous flaps from other locations of the patient's body.

Current criteria for matching recipients with donors in face transplantation include immune compatibility, skin color and texture, age, and gender.[10] The skin properties and age criteria are evaluated on a case-by-case basis, ultimately with the surgeon making a subjective decision about whether the match is aesthetically acceptable based on examination of the donor and recipient in person or in photograph. The aesthetic outcomes after face transplantation are not always optimal, partly because there is often an aesthetic mismatch between donor and recipient and partly because of the initial lack of muscle tone in the allograft. Unfavorable aesthetic results typically reflect an underlying functional discrepancy. For example, patients who receive either upper or lower jaw from the donor as part of their facial transplant have both aesthetic and functional (malocclusion) outcomes that are interdependent. As the global clinical experience with face transplantation grows, the availability of facial allograft donors is expected to increase, and immunosuppressive regimens for the recipients are expected to improve, expanding the practice of facial transplantation. Thus, evolved criteria for matching donors and recipients will be necessary to further optimize outcomes. Reproducible and inexpensive methods for predicting the aesthetic and functional compatibility of a donor-recipient pair will play an increasingly important role in this evolving field.

Due to ethical and logistical issues, studying the aesthetic and functional compatibility of donor-recipient matches in real face transplant cases is not feasible at this point in time. To circumvent this issue, we have developed and used a reproducible and inexpensive model of three-dimensional (3D) virtual face transplantation (VFT).[11] The model involves the reconstruction of high-resolution computed tomography (CT) scans of nontrauma patients, creation of virtual defects in donor and recipient models, and replacement of the recipient's defect site with corresponding tissues from the donor. The defects can be designed in various patterns and geometries. We have previously used this model to demonstrate that the transfer of facial appearance from donors to recipients in face transplantation is low.[11] In the present study, we used this model to evaluate correlations between the aesthetic outcome of face transplantation and anatomical differences in pretransplant craniofacial measurements performed in donor and recipient models.

Given the short amount of time available for the evaluation of a potential donor to a surgical team recovering a facial allograft, a simple guide like the one we describe here would be of great value. We investigated parameters that can be quickly and easily measured in a clinical setting to maximize the practicality of our approach. First, we quantified anthropometric soft-tissue landmarks in donors and recipients of VFT. In practice, identical measurements can be quickly and easily made on the bedside. We hypothesized that some or all of these anthropometric measurements would provide predictive power as to the perceived aesthetic outcome of donor-recipient VFT pairs. We had to additionally consider that soft tissues may be lacking in some face transplant candidates owing to the disfiguring injury. We thusly analyzed bony landmarks as well. We hypothesized that bony (ie, cephalometric) landmarks may provide additional predictive ability as to the aesthetic matching of donors and recipients of VFT. We chose various bony measurements, some of which do not have corresponding soft-tissue measurements. We made our bony measurements on CT scans, but they can be made on x-ray cephalograms as well.

The results of our study suggest that the matching of donors with recipients on the basis of soft and bony facial tissue measurements is a simple, low-risk, low-cost, high-benefit approach and can provide improved donor-to-recipient compatibility in facial transplantation.

METHODS

Scan Retrieval and VFT

Seventy-three 3D VFTs were performed using 143 de-identified high-resolution CT scans as described in detail elsewhere.[11] Donor-recipient pairs were excluded from the present study if the donor and/or the recipient pretransplant models were of insufficient resolution for accurate tissue measurements or if they did not have a neutral facial expression because this would confound the perception of disfigurement. After these exclusions were performed, we had a total of 61 VFTs available for analysis.

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Reviews

We recruited 20 independent reviewers as follows: 2 male and 2 female layperson reviewers with a minimum education of a high school diploma from each of 5 age groups (20–29, 30–39, 40–49, 50–59, and 60–69). Each of these reviewers was given a task to independently evaluate the level of disfigurement in the posttransplant 3D models. Each reviewer was shown each posttransplant 3D model and asked to rate their perception of the level of disfigurement for each model as only one of the following options: "very disfigured," "slightly disfigured," "not disfigured," or "not sure."

Soft-tissue Measurements

Dolphin Imaging Software (Chatsworth, Calif.) was used to measure landmarks on each reconstructed 3D donor and recipient soft-tissue models (Fig. 1). Vertical measurements (total facial height, trichion-to-nasion distance, nasion-to-subnasale distance, and subnasale-to-menton distance) and horizontal measurements (zygomatic width, chelion width, alar width, exocanthal width, and endocanthal width) were recorded for each donor and recipient model.

Bony Tissue Measurements

Dolphin Imaging Software was also used to measure bony landmarks on the donor and recipient. Two-dimensional cephalograms of each donor and recipient were constructed, and measurements of facial width, facial height, facial depth, and important craniofacial angles were made. Lateral measurements included middle-third facial height, bottom-third facial height, facial depth, as well as measurements of the angles between the sella-nasion plane and nasion-A point plane, sella-nasion plane and nasion-B point plane, A point-nasion plane and nasion-B point plane, palatal plane and mandibular plane, occlusal plane and mandibular plane, and sella-nasion plane and mandibular plane. An example of these measurements is shown in Figure 2.

Statistical Analyses

Corresponding soft-tissue and bony measurements were compared between each donor-recipient pair, and the absolute differences were recorded. Correlations between the reviewers' ratings of level of disfigurement for each posttransplant model with the absolute differences in each of the measurements performed were investigated. Logistic regression models were generated using SAS/STAT statistical software (Cary, N.C.) to determine the odds ratios (ORs) associated with each of the various measurements.

For the soft-tissue measurements, multivariate logistic regression was used to look at prediction of discrete outcome of reviewer's response ("very disfigured" to "not disfigured" or "mildly disfigured") by

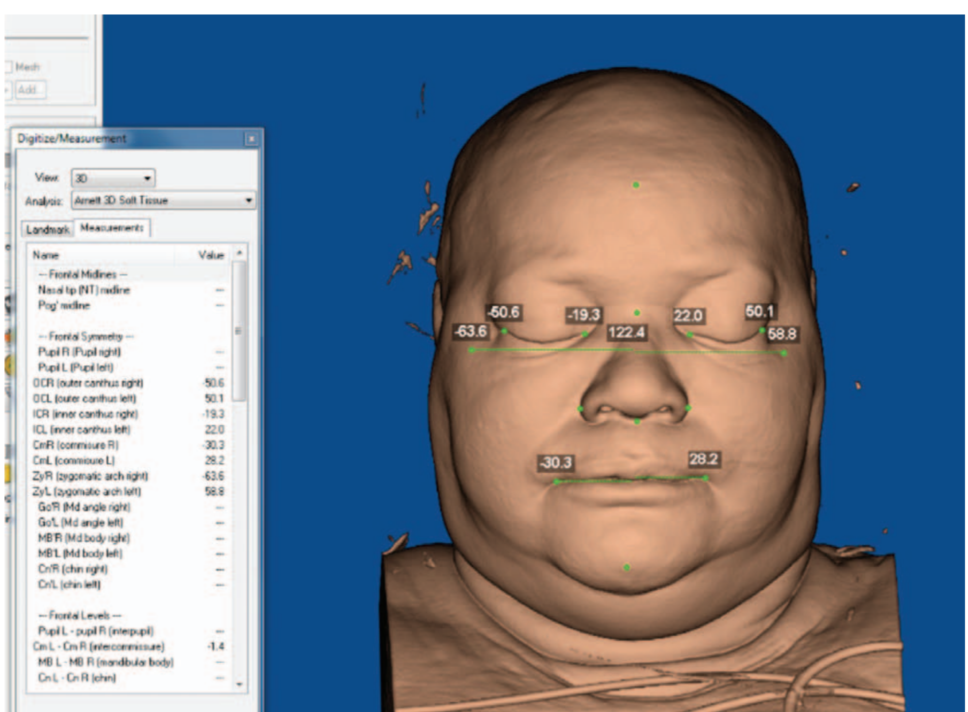

Fig. 1. Example of soft-tissue measurements of virtual models. Each recipient and donor pretransplant model was loaded into Dolphin surgical planning software for measurement of 9 common soft-tissue distances in both horizontal and vertical directions.

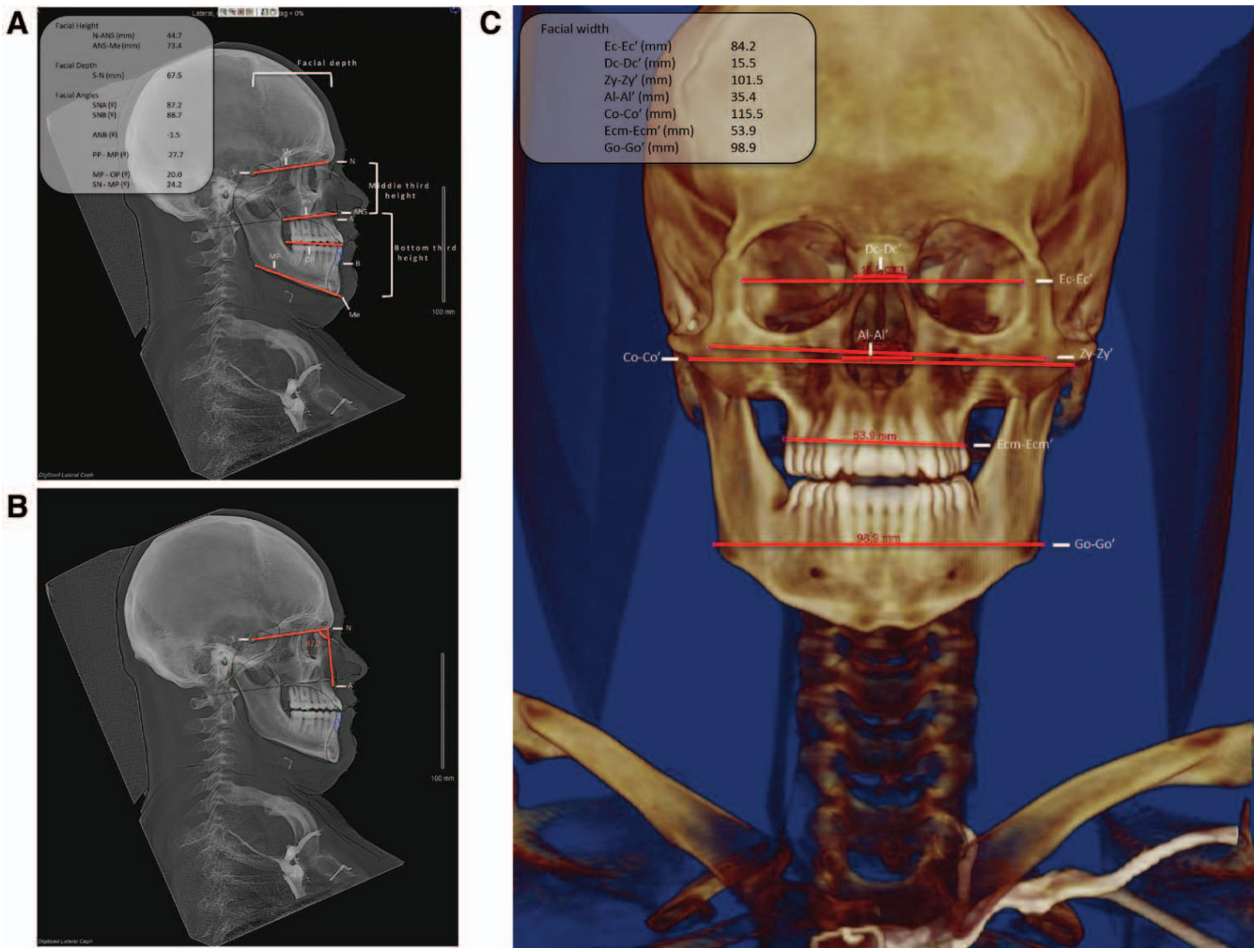

Fig. 2. Example of bony measurements of virtual models. Each recipient and donor pretransplant model was loaded into Dolphin surgical planning software for measurement of 9 common bony distances in both horizontal and vertical directions (A). Conversion of models into lateral cephalograms (B and C) with the software facilitated measurements of 6 cephalometric angles and measurement of facial depth.

the predictive variable of absolute soft-tissue measurement difference between donor and recipient. This controlled for clustering by presentation, gender, age difference between donor and recipient, and surgical pattern of VFT, enabling us to see which ORs were significant given a 1-mm increase in absolute difference between donor and recipient for each measurement. We chose 1-mm absolute difference because of its clinical relevance (ie, a difference we can detect by simple measurements at the patient's bedside).

For the bony measurements, a similar multivariate logistic regression model was used to look at prediction of discrete outcome of reviewer's response ("very disfigured" to "not disfigured") by absolute bony measurement difference between donor and recipient while controlling for the same variables as described above.

Interreviewer reliability was tested by calculating intraclass correlation coefficients (ICCs). An ICC = 1 denotes perfect agreement between reviewers.

RESULTS

Reviewer Response Characterization

The reviewer tasks generated a total of 1433 responses (Table 1). There were only 18 "not sure" responses.

Soft-tissue Measurement Correlation

Five of the 9 evaluated soft-tissue measurements were predictive of posttransplant models being rated "very disfigured" compared with "not disfigured" or "mildly disfigured" and were as follows (Fig. 3): trichion-to-nasion facial height (OR, 1.106; 95% confidence interval, CI, 1.066–1.148), endocanthal width (OR, 1.096; 95% CI, 1.051–1.142), exocanthal width (OR, 1.067; 95% CI, 1.036–1.099), mouth/chelion width (OR, 1.064; 95% CI, 1.019–1.110), and subnasale-to-menton facial height (OR, 1.029; 95% CI, 1.003–1.056).

Table 1. Number of Reviewers Who Rated Each VFT According to a 4-choice Answer

Pattern	VFT No.	Very Disfigured	Slightly Disfigured	Not Disfigured	Not Sure
1	1	0	13	7	0
3	2	0	4	15	1
2	3	0	9	10	1
1	4	3	14	3	0
3	5	9	10	1	0
1	6	6	10	4	0
1	7	5	12	2	1
3	8	1	1	15	0
2	9	6	9	5	0
1	10	7	9	4	0
1	11	2	10	6	2
3	12	3	14	3	0
1	13	1	9	11	0
2	14	4	9	7	0
3	15	0	6	14	0
1	16	0	10	9	1
2	17	10	8	2	0
2	18	2	7	3	0
2	19	6	7	7	0
1	20	0	8	12	0
1	21	2	9	9	0
2	22	1	7	12	0
3	23	5	11	4	0
2	24	4	8	8	0
2	25	2	6	12	0
3	26	0	13	4	0
1	27	4	8	8	0
3	28	12	5	1	1
2	29	0	3	17	0
3	30	2	9	9	0
2	31	4	10	6	0
2	32	1	8	11	0
2	33	0	4	15	0
3	34	14	6	0	0
1	35	9	6	5	0
1	36	3	13	4	0
1	37	0	9	11	0
1	38	0	3	17	0
2	39	1	11	8	0
1	40	7	6	7	0
2	41	0	15	5	0
3	42	6	14	0	0
3	43	1	5	13	1
2	44	5	9	6	0
2	45	0	1	17	1
1	46	6	10	4	0
1	47	2	2	15	1
2	48	10	8	1	1
2	49	0	11	9	0
3	50	0	8	12	0
3	51	12	6	2	0
2	52	12	5	3	0
2	53	1	1	17	1
2	54	2	7	11	0
3	55	10	9	1	0
1	56	8	9	3	0
3	57	0	9	8	0
1	58	1	8	9	0
1	59	2	9	8	1
1	60	3	12	5	0
3	61	5	8	4	0
2	62	1	5	13	1
3	63	6	9	4	1
1	64	0	3	14	0
2	65	4	11	5	0
3	66	0	10	10	0
3	67	8	7	5	0
3	68	2	9	9	0
2	69	0	10	9	1
2	70	6	8	6	0
1	71	3	9	7	1
3	72	4	12	3	1
3	73	1	11	8	0

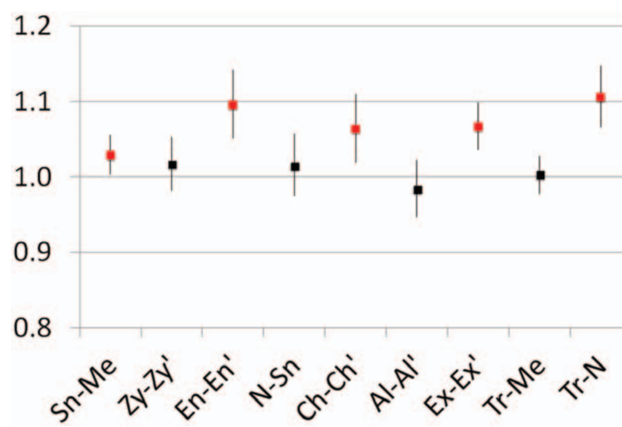

Fig. 3. Odds ratios of various absolute soft-tissue measurement differences between donor and recipient correlating with disfigurement. Odds ratios are shown as boxes with 95% confidence interval tails. Distances that significantly predicted discrete outcome of rater response ("very disfigured" to "not disfigured" or "mildly disfigured") are colored with a red box. Vertical soft-tissue measurements: Tr-Me (trichion-to-menton), total facial height; Tr-N (trichion-to-nasion), upper third height; N-Sn (nasion-to-subnasale), middle third height; and Sn-Me (subnasale-to-menton), bottom third height. Horizontal soft-tissue measurements: Ex-Ex′, outer eye width; En-En′, inner eye width; Zy-Zy′, cheekbone width; Al-Al′, alar base/nose width; and Ch-Ch′, chelion/mouth width.

Bony (Cephalometric) Measurement Correlation

Three of the 16 evaluated bony (celphalometric) measurements were predictive of posttransplant models being rated "very disfigured" compared with "not disfigured" and were as follows (Fig. 4): inner orbit width (OR, 1.039; 95% CI, 1.009–1.069), palatal plane/occlusal plane angle (OR, 1.148; 95% CI, 1.047–1.258), and sella-nasion/mandibular plane angle (OR, 1.079; 95% CI, 1.013–1.150).

All ICCs were significantly greater than 0, meaning that there was significant agreement among reviewers. However, because all ICCs were less than 0.5, there is still a good amount of variability among reviewers reviewing the same VFT (ie, all reviewers did not agree on the appearance). We believe this was to be expected, as the situation is not different than if one were to ask a group of people to rate the

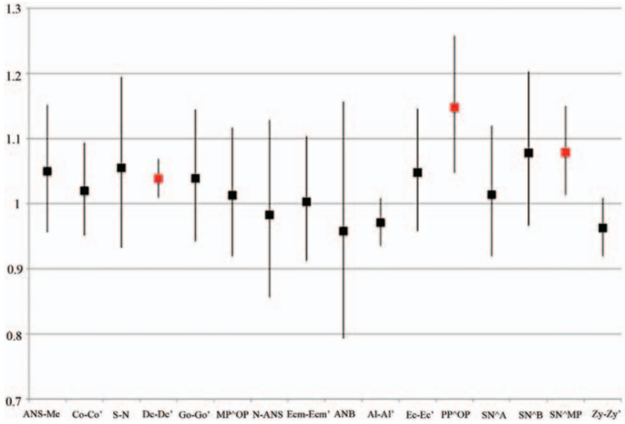

Fig. 4. Odds ratios of various absolute bony measurement differences between donor and recipient correlating with disfigurement. Odds ratios are shown as boxes with 95% confidence interval tails. Distances that significantly predicted discrete outcome of rater response ("very disfigured" to "not disfigured") are colored with a red box. Vertical bony measurements: N-ANS (nasion-to-anterior nasal spine), middle third height; and ANS-Me (anterior nasal spine-to-menton), bottom third height. Horizontal bony measurements: Ec-Ec′, outer orbit width; Dc-Dc′, inner orbit width; Co-Co′, condylar width; Zy-Zy′, zygomatic width; Al-Al′, alar base/nose width; Ecm-Ecm′, mouth width; and Go-Go′, bigonial/jaw width. Angles and depth: MP^OP, mandibular plane-occlusal plane angle; ANB, A point-nasion-B point angle; PP^OP, palatal plane-occlusal plane angle; SN^A, sella nasion-A point angle; SN^B, sella nasion-B point angle; SN^MP, sella nasion-mandibular plane angle; and S-N (sella-nasion), facial depth.

attractiveness of normal people walking down the street—one would get variability in that also. Agreement is higher among older (age > 50) reviewers.

DISCUSSION

Face transplantation is a relatively new field where a number of important questions remain unanswered, some of them with regard to how to best match donors with recipients for optimum aesthetic and functional outcomes. As face transplantation is becoming more commonplace, new studies are increasingly focused on how to best optimize the operation. These studies must be able to provide a large sample population and a realistic simulation of the facial transplant outcomes to provide statistically significant and generalizable conclusions. Given the ethical issues associated with maintaining anonymity of donors and the relatively low volume of cases available for study, research posed at answering these questions must be elegantly designed to use realistic models of human facial transplantation rather than actual donors and recipients. To date, some studies have addressed these challenges by performing face transplant simulations with cadavers.[12–15] Dorafshar et al[16] recently reported their experience with the use of computerized planning on a series of 10 mock facial transplants on cadavers. Preoperative planning ensured a good donor-recipient skeletal match. Although the study by Dorafshar et al[16] provides important insight on how transplants can be performed efficiently, it does not address how to prioritize matching donors and recipients for an optimal outcome. There are a number of practical and ethical limitations to the use of cadaver studies. The number of available cadavers is limited, and the process of performing a transplant with a human head is lengthy and expensive. Furthermore, the results of a cadaveric transplant may seem grotesque, which may make an independent, unbiased review of the outcome difficult to accomplish. Our study represents the first attempt to quantitatively predict the aesthetic and functional compatibility of a donor-recipient pair based on simple, inexpensive, easily attainable models and measurements.

Our study is further unique in that it links quantitative analysis of facial measurements with the unbiased population's perception of aesthetic outcome. By asking independent reviewers to assess the aesthetic outcome of a VFT, we can obtain richer outcome information than through strictly quantitative analysis. The aesthetic outcome of a face transplant, as perceived by the general population, is crucial in determining the aesthetic suitability of a face transplant, as these patients will ultimately be facing the general population. Information gathered from independent reviewers therefore makes the analyses we conduct relevant to the clinical question of aesthetic suitability.

In this study, we found 5 and 3 landmarks in soft tissue and bony tissue, respectively, where discordances between recipient and donor were correlated with a high degree of disfigurement. The soft-tissue landmarks can easily be measured at bedside for both donor and recipient, whereas the bony tissue landmarks may require the availability of radiological studies in the patients' files. CT scans of face transplant recipients are always obtained as part of the preoperative evaluation process; however, craniofacial imaging of the donor may not be readily available or feasible at all donor institutions. Thus far, in our experience with 5 facial transplants at Brigham and Women's Hospital, we have not used high-resolution CT angiograms of the allograft donors for surgical planning. Looking retrospectively, these data would not have been available for all 5 donors at the times of transplant. However, we believe that given enough clinical relevance is demonstrated, the organ processing organization can incorporate relatively simple protocols of craniofacial imaging to the donor's evaluation process for facial transplantation.

LIMITATIONS

The virtual face transplant model is not without its own limitations. As with a cadaveric transplant, the VFT is not a live facial transplantation. In its current state, VFTs do not allow for analysis of the resulting muscle or nerve function. Additionally, after face transplantation, numerous changes and revisions may change the ultimate aesthetic outcome from its initial appearance. Thus, VFTs portray only an approximation of how a face transplantation may appear and only at one point in time. Despite these limitations, our study represents the first attempt to offer a new tool that can be used to improve outcomes of future face transplantations. Transplant teams can focus on landmarks with the highest predictive value to create an algorithm that quickly assesses whether donor-recipient matches will produce favorable outcomes. Knowledge of both important soft-tissue and bony tissue landmarks lends teams more flexibility and comprehensiveness: in actual practice, soft-tissue measurements are more easily and inexpensively analyzed than bony tissue measurements, but bony measurements provide extra information about the relation of landmarks to each other.

Because of donor scarcity and the importance of difficult immune compatibility considerations, we acknowledge that the current state of face transplantation generally does not allow us to "pick and choose" donor candidates for specific recipients. However, as awareness improves in the general public, we expect to see expansion of the donor pools, and as we learn more about immune compatibility and modulation, we will see increased volumes of candidates for face transplantation. We report our findings in anticipation of a need for improved criteria for facial allograft allocation.

CONCLUSIONS

Five soft-tissue measurements that can be performed at the bedside and 3 bony measurements that can be derived from craniofacial radiological studies were found to significantly correlate with the degree of perceived disfigurement following VFT. These findings provide a new, simple tool for face transplant surgeons to predict the aesthetic outcome of facial transplantation and, in due time, generate evolved and improved criteria for the allocation of facial allografts.

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