INTRODUCTION

Thousands of patients in the world suffer from devastating loss of complex facial tissues.1-3 These defects frequently compromise quality of life (QOL) by impairing vital and social functions, which may ultimately lead to social isolation due to severe facial disfigurement.4,5 Midfacial deformities are among the most complex defects to reconstruct. Conventional reconstruction traditionally uses local or distant free tissue transfer to replace destructed tissue. In these cases, functional rehabilitation and replication of human facial features are hardly possible using conventional methods.5,6 Facial vascularized composite allotransplantation (fVCA) has emerged as an alternative that can achieve both functional and esthetic rehabilitation (Figure 1).7

Initial outcome reports after fVCA revealed encouraging results of this reconstructive option.4,8,9 However, complications related to immunosuppression and chronic rejection may partially negate the restorative potential of fVCA.10 Currently, most scientific evidence in this field is derived from small case series and case reports. In addition, the potential benefits of fVCA are limited by the available data on long-term outcome after this procedure. Few studies have reported long-term outcomes after fVCA, and the majority of these reports involve single-center experiences.2,3,8,9 As such, it is difficult to accurately estimate the risks and benefits of fVCA. Long-term outcome data are essential to help guide patient selection and counseling in the context of fVCA.

Methods. We conducted a systematic review of PubMed/MEDLINE databases in accordance with PRISMA guidelines. English full-text articles providing data on at least 1 unique fVCA patient, with ≥3 years follow-up, were included. Results. The search yielded 1812 articles, of which 28 were ultimately included. We retrieved data on 23 fVCA patients with mean follow-up of 5.3 years. More than half of the patients showed improved quality of life, eating, speech, and motor and sensory function following fVCA. On average, the patients had 1 acute cell-mediated rejection and infectious episode per year. The incidence rates of acute rejection and infectious complications were high within first-year posttransplant but declined thereafter. Sixty-five percent of the patients developed at least 1 neoplastic or metabolic complication after transplantation. Chronic vascular rejection was confirmed in 2 patients, leading to allograft loss after 8 and 9 years. Two patient deaths occurred 3.5 and 10.5 years after transplantation due to suicide and lung cancer, respectively. Conclusions. Allograft functionality and improvements in quality of life suggest a positive risk-benefit ratio for fVCA. Recurrent acute rejection episodes, chronic rejection, immunosuppression-related complications, and heterogeneity in outcome reporting present ongoing challenges in this field.

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derived from short-term technical feasibility reports or is limited to single-center experiences.  

Fifteen years after the first partial fVCA in 2005, analysis of long-term outcomes becomes possible. The aim of this study was to merge the myriad of published long-term outcome data from different centers around the world to better appraise the risks and benefits of fVCA.

MATERIALS AND METHODS

Search Strategy

This study was an exempt from institutional review board approval. The systematic literature review was completed on November 15, 2019. PubMed/MEDLINE databases were searched, following the recommendations from the 2009 PRISMA Statement. The search strategy terms were “facial transplantation,” “vascularized composite allotransplantation,” and “facial transplant outcomes.” Articles describing human fVCA written in English and published between November 2005 and November 2019 were included. Only original articles reporting on patients with at least 3 years of posttransplant follow-up were included. The literature search and data extraction were performed by 2 independent investigators (BT, OA). In cases of disagreement, a third investigator (BK) was consulted to resolve discrepancies.

The following data points were extracted: age of donor and recipient, gender, race, mechanism of injury, extent of fVCA (full/partial), inclusion of tooth-bearing bone, induction/maintenance immunosuppression regimen, panel-reactive antibody, HLA mismatch, Cytomegalovirus (CMV)/Epstein-Barr Virus serostatus, total follow-up time, QOL measures, eating, breathing and smelling status, oral competence, mouth opening, speech, motor and sensory function of the allograft, acute and chronic rejection episodes, and complications (infectious, metabolic, neoplastic).

Data Analysis

Both quantitative and qualitative outcome data were recorded and used for analysis. Due to interinstitutional differences and heterogeneity in outcome reporting, we had to introduce 3 qualitative outcome groups for the following variables: QOL, ability to eat, oral competence, mouth opening, speech, sensory and motor function. These qualitative outcome groups were defined as follows: “improved,” “impaired,” and “not reported.” This was necessary to allow comparison and aggregation of outcomes from different centers (Table S1, SDC, http://links.lww.com/TP/C53).

Categorical data are reported as counts (%); continuous data are reported as means ± SDs. Incidence rates were calculated using the number of events divided by the sum of years at risk for each fVCA recipient during the 2 periods of interest: first posttransplant year (early period) and the period thereafter up to the end of follow-up (late period). Incidence rates are expressed as the number of events per transplant-year (TY). Data from included articles were analyzed using IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp).

RESULTS

Study Participant Characteristics

Details of the included studies are shown in Table 1. All investigations were rated level 4 with the modified rating from the Oxford Centre for Evidence-based Medicine

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Quality of Life

QOL assessment was heterogeneous across studies (QOL instruments and respective patient data are detailed in Table S2, SDC, http://links.lww.com/TP/C53). The self-reported EuroQol Group-5 Dimensions Visual Analogue Scale (EQ-5D VAS) was completed with 6 patients, the Center for Epidemiologic Studies Depression Scale (CES-D) score was used with 6 patients as well, the Facial Disability Index helped to measure QOL in 2 patients, the Psychological Adjustment to Illness Scale—Self Report (PAIS-SR) was completed by 1 patient and the 36-Item Short Form Survey (SF-36) was completed in 6 patients. Overall, 65.2% of fVCA recipients showed an improvement in their QOL after transplant; 13.0% of patients reported a decrease in their QOL (Figure 3). For 34.8% of recipients, QOL was assessed subjectively without use of a standardized metric (Figure S1, SDC, http://links.lww.com/TP/C53). 21.7% of recipients had no data reported on their QOL at all (Figure 3).

Eating

After fVCA, 100% of the patients depending on gastrostomy (n = 7) were decannulated. 69.6% of the cohort either was not gastrostomy dependent or was not reported to have had a gastrostomy tube. Eating, oral competence (closure of the lips), and mouth opening were improved in 95.7%, 39.1%, and 21.7% of fVCA recipients, respectively. An impairment in eating, oral competence, and mouth opening was reported in 4.3%, 13.0%, and 8.7% of the patients, respectively. A total of 47.9% and 69.9% of patients did not have any data reported on their oral competence and mouth opening, respectively (Figure 3).

Breathing

Following fVCA, 100% of the recipients who needed tracheostomy before transplant (n = 9) were successfully decannulated. 60.9% of recipients either did not have tracheostomies, or information about tracheostomy dependence was not reported (Figure 3).

Allograft Function

Improvements in communication were seen in 56.6% of recipients. However, 13.0% remained with impaired speech (Figure 3). Five patients’ speech (21.7%) was assessed with the speech intelligibility test, during which a trained, unfamiliar listener evaluates each sentence (Table S2, SDC, http://links.lww.com/TP/C53). 78.3% of participants did not have their speech assessed objectively after fVCA (Figure S1, SDC, http://links.lww.com/TP/C53). 30.4% of patients had no data reported on their speech (Figure 3).

Facial sensation was measured using 2-point discrimination (n = 7), calorimetric (hot and cold) (n = 9), or Weinstein monofilament testing (n = 10) (Table S2, SDC, http://links.lww.com/TP/C53). Improvements in graft sensation were recorded in 69.6% of recipients. Impairment in sensory function was reported in 8.7% of the participants (Figure 3). 69.6% of the patients did not have their sensory abilities measured via 2-point discrimination; 60.9% did not have calorimetric testing; 56.5% did not have Weinstein monofilament testing (Figure S1, SDC, http://links.lww.com/TP/C53).

Motor function was measured using Daniels & Worthingham Manual Muscle Testing (n = 7) or the electromyography (EMG) (n = 3) (Table S2, SDC, http://links.lww.com/TP/C53). Over time, 82.6% of fVCA recipients had improvements in their motor function. Patients with motor impairment in their graft and those with no recorded data on motor function represent each 8.7% of the cohort (Figure 3). 56.5% of patients did not have their motor function assessed quantitatively with at least 1 of

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the motor function tests mentioned above (Figure S1, SDC, http://links.lww.com/TP/C53).

Immunosuppression and Rejection

All patients who had induction immunosuppression reported (73.9%) were induced with antithymocyte globulin. 26.1% of patients included in this study had no data reported regarding their induction regimen, and 8.7% of patients had a donor bone marrow infusion as addition to the antithymocyte globulin. In 95.7% of the patients, maintenance immunosuppression consisted of mycophenolate mofetil or mycophenolic acid, tacrolimus, and prednisone (Table 2).

Overall, patients had 0.92 acute rejection episodes per TY. The incidence of acute rejection episodes was particularly

FIGURE 2. Systematic review flow chart.
high in the first posttransplant year (2.15 events/TY) and declined thereafter (1.06 events/TY) (Figure 4). In the first posttransplant year, 56.5% of patients had at least 1 rejection episode. During the second posttransplant year, 26% of patients had 1 or more rejection episodes, compared with 47.8% of the patients during the third posttransplant year (Figure S2, SDC, http://links.lww.com/TP/C53). According to Banff classification for skin-containing composite tissues, grade II and III cell-mediated rejection (CMR) episodes had the highest incidence rates during both early (£1 y) and late (>1 y) periods (Figure 4).

Adjustment of maintenance immunosuppression and steroid boluses were frequently used to treat acute rejection episodes (Figure 5). Four antibody-mediated rejection (AMR) episodes were recorded; they were managed with various combinations of plasmapheresis (n = 4), intravenous immunoglobulin (n = 3), rituximab (n = 3), eculizumab (n = 2), and bortezomib (n = 3) (Table S2, SDC, http://links.lww.com/TP/C53). One late AMR episode with de novo HLA donor specific antibodies was associated with allograft loss.

Chronic skin changes (eg, papillary dermal sclerosis, adnexal atrophy, lichenoid aspect) were observed in 30.4% of patients, but they did not correlate with decreased allograft function (Table S2, SDC, http://links.lww.com/TP/C53). Chronic vascular rejection was confirmed in 2 patients, which led to allograft loss after 8 and 9 years.

**Infectious Complications**

The patients had an overall 1.12 infectious episodes per TY. The high-incidence rate in the first posttransplant year (4.3 events/TY) declined during the following years (0.4 events/TY). Bacterial infections had a higher incidence rate (0.59 events/TY) than viral (0.49 events/TY) and fungal infections (0.14 events/TY) (Figure 6). Surgical site infections were the leading cause of early onset postoperative infectious complications. CMV was the most common opportunistic viral infection (26.0%).

**Metabolic and Neoplastic Complications**

Transient nephrotoxic episodes (TNE) (30.4% of recipients), dyslipidemia (21.7% of recipients), chronic kidney disease (CKD) (13.0% of recipients), hypertension (13.0% of recipients), and diabetes mellitus (13.0% of recipients) were the most common de novo metabolic complications following transplantation (Figure 7).
Three cases of neoplastic complications were reported. Posttransplant lymphoproliferative disease (PTLD) (n = 1), lung cancer (n = 1), and in situ cervix carcinoma (n = 1) each occurred in 4.3% of patients (Figure 7). The PTLD occurred in an Epstein-Barr Virus–negative recipient who received allograft from Epstein-Barr Virus positive donor.

Overall, 65.2% of the FVCA cohort developed at least 1 neoplastic or metabolic complication after their transplantation (Figure 7). Patients who developed metabolic complications represented 60.9% of the cohort, and those who developed a neoplastic complication represented 8.7% of the cohort. 34.8% of patients did not have any data reported on the neoplastic and/or metabolic complications they might have developed.

**DISCUSSION**

FVCA is an accepted reconstructive option for selected patients with severe facial disfigurement. To date, the
long-term risks and benefits are not sufficiently defined. This is mainly due to the lack of agreement on outcomes measures and difficulty defining success and failure resulting in low number of large-cohort, long-term outcome reports. We herein provide a comprehensive multicenter summary of reported outcomes from scientific literature. We summarize data on 23 patients from 6 centers around the world.

Quality of Life

Our summary of literature revealed that fVCA was able to improve daily life activities such as eating, breathing, speaking, and social interaction.17,35 In fact, all of the aforementioned improvements may have contributed to a sustained improvement in QOL after fVCA.4-6,11,12,17,27,29,32,33,35 Common to all centers is the satisfaction and renewed sense of identity patients experience as they integrate their allografts to be parts of their bodies.11,13,17,22,23,33 fVCA not only helps to restore physical identity but also an individual's social identity by facilitating social integration.13,17,33,37 Social integration (work, family, and community) appears to reduce the risk of clinical depression and reinforces immunosuppressant compliance.6,12,13 Reasons that some patients experienced lower QOL outcomes may include the presence of preexisting psychiatric conditions (eg, depression, anxiety, posttraumatic stress disorder) and the impact of posttransplant complications on patients’ lives (eg, immunosuppression-related complications, discomfort associated with CMR episodes). The burden that frequent follow-ups, lab draws, and hospitalizations related to treatment of complications bring to patients’ lives should not be underestimated. To date, there is no face-transplant-specific QOL questionnaire. Therefore, QOL measures may have been influenced by transplant-unrelated issues. Future research should focus on the development of face-transplant-specific QOL metrics to better quantify the procedure-related QOL changes. Such tools could guide the selection of patients who have the highest potential to benefit from the procedure.
The fVCA cohort in this study showed a reported long-term mortality rate of 8.7%. Two individuals died, 1 due to lung cancer (the patient was a long-time smoker) and 1 due to suicide. It is, however, important to note that the mortality in this study might be underestimated because of the patients in whom death occurred before 3 years of follow-up. Indeed, 4 deaths due to suspected noncompliance, cancer recurrence in an HIV+ patient, sepsis combined with anoxic brain injury due to occluded tracheostomy, and lymphoma with respiratory failure were previously reported in the literature. More recently, a case report describing the death of a fVCA recipient as a result of hepatocellular carcinoma secondary to an uncontrolled hepatitis-C-virus infection 10 years after transplantation was published. Moreover, 2 additional deaths were communicated through different media outlets. One patient from Turkey died of undisclosed reasons, approximately 4 years posttransplant, and 1 patient from United States deceased 12 years after surgery due to an infection unrelated to transplant. Owing to the nonlife-saving nature of this procedure, every fatal event must be critically appraised. Therefore, patient-related factors (eg, noncompliance, pre-existing psychiatric, and medical issues) necessitate rigorous medical, psychiatric, and social-support screening before transplantation. This will help minimize the risk of psychiatric illness and suicide following fVCA.

**Allograft Function**

Restoration of facial motor and sensory function is one of the main goals of fVCA. A significant number of patients in this study showed improvements in motor and sensory function following transplantation. However, the motor recovery assessment is not standardized in fVCA. Thus, new technologies such as the artificial intelligence-driven software evaluation of facial movements could help to solve this issue. Additionally, another considerable achievement of fVCA was related to oral food intake which improved in 95.7% of the recipients. These data show that fVCA can restore the stomatognathic system to a degree that makes gastrostomy and tracheostomy removal possible. Considering the potentially life-threatening sequelae associated with long-term tube placement (eg, pneumonia, fistulation, and sepsis), this is a major benefit associated with this procedure.

**Infectious Complications**

This study highlights the importance of rigorous clinical surveillance in the early phase posttransplant. Local infectious complications involving the allograft (eg, cellulitis, sinuitis, surgical site infections) and opportunistic viral pathogens (CMV, HSV) were among the most common. These findings are in line with reports from the International Registry on Hand and Composite Tissue Transplantation (IRHCTT). Both fVCA recipients from this study and upper extremity allotransplantation (UEA) recipients from the IRHCTT registry showed a gradual decline in infectious complications over time. The incidence rate of infectious complications declined after the first posttransplant year, from 4.3 to 0.4 events/TY for fVCA patients and 3.27 to 0.15 events/1000 transplant-days for UEA recipients. One reason that could explain an overall higher incidence rate of infectious complications for fVCA recipients than UEA recipients is the presence of oral mucosal tissue in fVCA. Our data warrant particular attention to infectious complications in fVCA compared with UEA and

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**FIGURE 7.** De novo metabolic and neoplastic complications after facial vascularized composite allotransplantation. DM, diabetes mellitus; PTLD, posttransplant lymphoproliferative disease.
SOT.50 We may need to adapt the current regimens to lower the overall incidence of infectious complications.28,36

Metabolic and Neoplastic Complications

According to published literature, 63.0% and 13.4% of kidney transplant (KT) recipients develop metabolic and neoplastic complications, respectively.21,32 These numbers are similar when compared with the fVCA cohort in our study (60.9% and 8.7% for metabolic and neoplastic complications, respectively). One reason explaining this finding could be that the maintenance immunosuppression regimens used in fVCA recipients are akin to the ones used in KT recipients. We also found that almost one-third of the fVCA recipients developed a TNE. This was mostly attributable to calcineurin inhibitor-based maintenance immunosuppression regimens and medications used to treat ongoing infections.21 Among the 7 patients who had a TNE, 3 developed CKD. Therefore, strategies to minimize kidney damage after fVCA should be an important part of the patient management.21 In summary, it appears that the long-term rates of metabolic and neoplastic complications in fVCA are comparable to the rates in other organ transplantations.

Acute and Chronic Rejection

We found an overall high-incidence rate of acute rejection episodes (0.92 events/TY) in our fVCA cohort. These numbers remarkably surpass the incidence rates in UEA (0.5 events/1000 transplant-days) and KT (0.17 events/1000 transplant-days), which were recently reported in a study from the IRHCTT registry.50 The relatively high-incidence rate of acute rejection after the first posttransplant year (1.06 events/TY) in fVCA could be potentially explained by poor adherence and tapering immunosuppression regimens to treat immunosuppression-related complications.31,53 These observations support the idea that in the long-term, medical teams should carefully consider tapering their patients’ immunosuppression regimens because it can potentially induce an increase of acute rejection episodes. The dose variation needed to sufficiently suppress the immune system between each CMR episode could also play a role. Indeed, the treatment response did not correlate with histological grades of rejection in our study, because adjustment of maintenance immunosuppression alone resolved 27.1% and 36.2% of all grade II and III CMR episodes, respectively. These findings highlight the need to investigate new acute rejection biomarkers that could complement the traditional histopathological and clinical assessment.4,52

Commonly, antibody-mediated vascular damage with de novo donor-specific antibodies can lead to allograft loss, and these aspects are considered to be one of the hallmarks of chronic rejection.19,23 However, there are currently no formalized criteria to diagnose AMR and chronic rejection in fVCA. Recently, it has also been suggested that chronic skin changes in fVCA could occur independently of allograft vasculopathy and be triggered by repeated CMR episodes. It is unclear whether chronic skin changes could represent an early stage of chronic rejection or they may be seen as a previously unrecognized type of chronic rejection.20,43 We need to deepen research in this field to reach consensus about a common definition of chronic rejection in fVCA. It is important to mention that, in the recent years, there has been a collaborative effort between worldwide groups to define chronic rejection in VCA recipients, which mainly comprises criteria such as histological findings and allograft function.56 Nevertheless, it is likely that chronic rejection might lead to face allograft loss in some cases and exit strategies including retransplantation or conventional reconstruction should be in place.57

Current immunosuppressive regimens are associated with significant morbidity and cannot efficiently prevent chronic rejection.5,18,20,26,27 Therefore, future research should also focus on developing immunosuppressive therapies with better side-effect profiles and the potential to reduce the rate of chronic rejection. These might include costimulation blockade, cell-based therapies, tolerance induction through mixed chimerism, IL-2 immunomodulation, or localized immunosuppression.58-63

Data Reporting

At the time of our literature review, approximately 39 fVCA patients should have at least 3 years of follow-up.2 However, our study reveals that long-term outcomes were reported for only 23 patients. There is a total of 16 patients that were excluded from the present study because they either did not meet the ≥3 years of follow-up requirement or were not reported in the peer-reviewed literature. Of the 16 excluded patients, 5 died due to the reasons described previously.36,38-42,44 Two patients were excluded because of the lack of peer-reviewed reports, including 1 patient receiving face transplant in Turkey66 and the other 1 in Spain.57,68 Another Spanish patient with 6 months of follow-up was reported to receive successfully a face allograft that was provisionally perfused through the recipient femoral vessels.69 The first full-face transplantation was also performed in Spain.70 At 16 months posttransplant, the patient required a LeFort I osteotomy to improve his dental occlusion and solid diet intake.71 Three American patients did not meet the inclusion criteria for our study. The first is a man transplanted in 2012 who had 3 acute rejection episodes at 2 years of follow-up,72,73 Through meeting abstracts and media releases, the patient was reported to have an end-stage-renal disease that necessitated living-donor kidney transplantation 7 years post-transplant.74-76 The second patient is a male who received a total face and scalp transplant in 2015. After adding rituximab into his induction immunosuppression, the patient did not encounter any acute rejection episodes or metabolic complications during the 2-year follow-up.76,77 The third patient operated in 2016 had 1 acute rejection episode at 8 months postsurgery and has been followed for 20 months in total.78 Two Polish patients, both operated in 2013, were not included in the study. The first is a male who received the world’s first immediate face transplant.79 The second is a female who was transplanted due to advanced neurofibromatosis.80 They were followed for 24 and 34 months, respectively, and the reports suggest positive outcomes.79-82 A favorable outcome was also documented for the first Finnish face-transplant recipient at 30 months of follow-up.83,84 Finally, a Russian male underwent fVCA in 2015. A 4-year outcome report has been published after the completion of this study’s literature review, describing a successful social rehabilitation of the patient.85

Interestingly, a not negligible number of the information could only be found in media or conference outlets, hence
limiting the data quality and the comparison with the 23 patients included in the present systematic review. This shows a relevant underreporting of outcomes in the scientific literature, which limits the generalizability of conclusions. Otherwise, the data from those less well-documented cases allow us to appreciate that fVCA was overall beneficial. Further, although quantitative outcome metrics are available (eg, speech, QoL, motor, and sensory function), they are not used in many patients, which highlights the importance of improving the quality of long-term outcomes reports. The presence of heterogeneous data in the scientific literature forced us to use a binary classification (improved versus impaired function) to simplify the results interpretation. This fact comprises a limitation in the present study and emphasizes the importance for medical centers to find a consensus on a metric for reporting their patients’ long-term outcomes. Traditionally, the IRHCTT collects data on fVCA recipients. The 2017 IRHCTT report provided outcomes from 30 fVCA recipients. Despite methodological differences, the data from patients in our study and the IRHCTT cohort show several similarities. Regarding immunosuppression, no difference has been observed between the groups. Both cohorts also had a higher incidence in acute rejection episodes and infections within the first-year posttransplant. Both groups reported 2 cases of chronic rejection. The most common metabolic complications were similar as well, including hypertension, hyperglycemia, TNE, and CKD. Four patients deceased in the IRHCTT cohort compared with 2 deaths in our cohort. Regarding the functional recovery, the absence of objective measurements makes the comparison between the cohorts challenging. However, both groups demonstrated an improvement in motor and sensory function compared with the pretransplant state. In the recent years, United Network for Organ Sharing (UNOS) started tracking data on VCA procedures. Reporting to UNOS is mandatory and may fill the data void for future analysis. The IRHCTT, on the other hand, has voluntary contribution and reports nonindividualized data. Moreover, the registry presents some limitations due to lack of or incomplete data submission from different teams. The ideal solution would be a multicenter study with a wide agreement over tracked outcomes. This would provide more robust scientific evidence about the risks and benefits of this life-improving procedure.

CONCLUSION

The reported fVCA long-term outcomes are predominately encouraging. Functional and esthetic restoration was achieved in most cases. While acute rejection and infectious complication rates are particularly high early posttransplant, other immunosuppression-related complications seem not to surpass those of SOT patients. Lack of procedure-specific outcome metrics and heterogeneity in outcome reporting present ongoing challenges and should be addressed in the future. To further refine the risk-benefit ratio by prolonging the longevity of the allorafts, it is necessary to better understand the mechanisms underlying acute and chronic rejection in fVCA.

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