



Genitourinary vascularized composite allotransplantation

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Purpose of review

Genitourinary vascularized allotransplantation (GUVCA) is gaining interest as a treatment option for patients with functional and aesthetic urogenital tissue loss. Only three cases have been done worldwide and research on the implementation and feasibility of this procedure is in an elementary state.

Recent findings

The psychosocial impact and ethical considerations with GUVCA are remote, particularly because of the intimate and personal nature of genital tissue. Though two of the three penile transplantation cases are considered successful, various unexpected factors and complications have been described alongside these successes. Treatment outcome depends on a complex combination of immunological, technical, and psychosocial components that will be different per individual case. Multidisciplinary evaluation and treatment protocols should be established to ensure that the quality of life in GUVCA recipients can be increased in a safe and ethical way.

Summary

Penile transplantation represents challenging new potential to improve phallus reconstruction in patients with severe genital tissue defects, but worldwide experience with GUVCA is limited. Controlled multicenter research is required to better define the risk/benefit ratio of this experimental yet promising treatment option.

Keywords

genitourinary vascularized composite allotransplantation, penis transplantation, phalloplasty, reconstructive transplantation

INTRODUCTION

Over the last 20 years, vascularized composite allotransplantation (VCA) has become an accepted treatment option for patients with functional and aesthetic tissue defects [1,2]. Indications for VCA are expanding from the upper extremity, face, and abdominal wall to the reconstruction of urogenital tissue in patients with genitourinary tissue loss from trauma or cancer, injuries often associated with profound psychosocial issues. Wounded warriors with such injuries, civilian trauma patients, and a subset of penile cancer patient survivors previously left with disfiguring or minimal residual penile function have furthered research and interest in genitourinary VCA (GUVCA), more specifically penile transplantation.

The first penile transplantation was performed in China in 2006, and is generally considered unsuccessful as the graft was explanted on postoperative day (POD) 14, reportedly due to psychological rejection of the penile allograft by the patient and his wife [3,4]. Almost a decade later, van der Merwe *et al.*

successfully transplanted a penile allograft to a 21-year-old recipient, who now has full urinary and sexual function and reportedly impregnated his girlfriend [5,6]. In May 2016, we performed the second successful GUVCA in a 64-year-old patient with subtotal penectomy after penile carcinoma. Our patient represents the third case in the world literature experience, and opens the discussion of GUVCA, possibly leading to consideration and implementation of more similar transplants in this complex yet important and deserving patient population [7]. We will review the recent developments in the field of

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KEY POINTS

- Genitourinary vascularized composite allotransplantation is a novel and holistic treatment option for devastating loss of urogenital tissue.
- Successful outcome after penile transplantation will require an effective combination of immunological, surgical, and psychosocial factors, and careful patient selection is essential.
- The range of complications described in the three penile allograft recipients, including the occurrence (Boston) and absence (South Africa) of acute rejection episodes, demonstrate that the risk profile of this innovative procedure is versatile, with the majority of short-term and long-term risks continuing to be unknown.
- To ensure clinical applicability and ethical conduct, collaborative guidelines, protocols, and evaluation strategies should be established for the preparation, evaluation, and performance of genitourinary vascularized composite allotransplantation.

GUVCA, and highlight the essential aspects in the implementation of a GUVCA service.

CURRENT THERAPIES FOR RECONSTRUCTION

Current treatment options for penile absence or for female-to-male transgender are all autologous tissue based, with or without implant placement for penile rigidity. The patient's reconstructive goals and the extent of urogenital defect determine the method of reconstruction, as no ideal technique exists that fits all patients in these categories. All reconstructive options share the ultimate goal of an aesthetically satisfactory and functional phallus, including the ability for standing micturition, tactile and erogenous sensibility and erectile function (sufficient for penetration and possibly in some cases, insemination). Much of what we currently understand about the limitations of autologous phalloplasty techniques not surprisingly comes from the gender affirmation surgery literature. In these patients, microsurgical free flap reconstruction has become the gold standard, with the radial free flap being the most commonly chosen technique. Other flaps include the anterolateral thigh flap, lattisimus dorsi myocutaneous flap, the groin flap, or the free fibular flap. Morrison *et al.* [8¹] recently published a comprehensive literature review of the available data on phalloplasty techniques and outcomes, which demonstrates relatively high satisfaction rates associated with these procedures yet also summarizes the wide

range of complications and functional limitations that these patients encounter. Each reconstructive option has advantages and disadvantages, and none of the available modalities fully addresses the ideal goals of phalloplasty. Inadequate autologous tissue substitutes for erectile and urethral tissue contribute to the complexity of urogenital reconstruction. For some patients, therefore, GUVCA may represent the ideal treatment option.

ETHICS OF ORGAN OR TISSUE DONATION AND TRANSPLANTATION

Reconstructive transplantation has provoked challenging yet important ethical questions and debates ever since its clinical reality in the 1990s. Although interest in VCA has been growing fast over the recent years, it is highly 'avant-garde' nature causes its progression, through ethical reservations, to occur at a case-by-case basis. Psychosocial aspects, like quality of life, body image, and patient well being, play significant roles in the risk/benefit ratio of reconstructive transplants [9²,10]. Unlike visceral organ allografts, most VCAs have a visible skin component, which increases the implications for the recipient's 'sense of self' [9²]. As noted by Kunmig and Jowsey-Gregoire, GUVCA represents an even greater personal identity and involves an additional function of physical intimacy that may extend its implications to previous partners of the donor and future partners of the recipient. Although GUVCA may be the optimal treatment option for some patients, careful consideration is needed in educating potential candidates to prevent misconceptions regarding the risks of these experimental procedures [11³]. Side-effect profiles of life-long immunosuppression can result in significant morbidity but many patients will still accept these risks for the improved function and aesthetics resulting from a successful GUVCA. Ensuring realistic patient expectations is essential, however, not only for ethical reasons, but also to ensure postoperative success. An extensive informed consent process guided and overseen by an Institutional Review Board is crucial for GUVCA. An experienced transplant program considering the implementation of GUVCA should leverage well established solid organ transplant program protocols (e.g. for patient screening criteria, informed consent forms, patient education materials, etc.) and regulatory guidelines (In the USA—United Network for Organ Sharing (UNOS) compliance, etc.) in order to ensure careful execution of this multidisciplinary endeavor [9²,12⁴,13,14]. UNOS oversight is crucial and should be established before solely institutions with profound solid organ transplant programs can implement a challenging program like GUVCA.

SELECTION CRITERIA AND CANDIDACY

Genitourinary VCA should be approached as a holistic treatment option, encompassing a series of patient-specific issues, and not as just a single surgical reconstruction procedure. Selection and evaluation of recipient candidates is a lengthy multimodal process, for which a dedicated multidisciplinary transplant team is paramount. A GUVCA team should include a variety of experts that together have extensive urological, (micro)surgical, transplant, psychosocial, and ethical experience. Superlative coordination of specific patient and treatment domains is required.

The assessment process of potential candidates can be difficult due to the lack of instruments to fully measure the impact of urogenital tissue loss and infertility [9¹¹,10]. The patient's motivation for GUVCA should be extensively analyzed through a customized psychosocial evaluation protocol [9¹¹,10]. Preoperative evaluation should include: adaptation and coping with previous trauma and/or absence of urogenitalia, sexual and relational history, medical compliance history, substance abuse history, social support, financial resources, decisional capacity, desired goals, expected outcome, health literacy on transplantation, and the understanding and acceptance of the penile transplant risks (in particular, regarding the need for life-long immunosuppressive medication [9¹¹,15¹²]). In addition to stringent selection criteria for GUVCA candidacy, justifications to the Institutional Review Board should be made for the recipient. At-risk candidates should be identified, counseled, and possibilities to increase their eligibility should be explored, preferably when GUVCA has developed increasing feasibility as a treatment option. Jowsey-Gregoire and Kunmig [15¹²] have suggested a Transplant Collaborative Care model, which would facilitate optimal candidate screening through an improved evaluation process. Such a model could be customized to the needs of specific subpopulations within VCA, and would deemphasize the importance of a one-time instrument evaluation patient candidacy while incorporating the longitudinal nature of transplant case as typically practiced by transplant professionals. Assuring careful assessment of demarcated transplant domains; the patient candidate would be evaluated at specific intervals, which allows comparison across multiple centers. Such a standardized psychosocial evaluation tool for VCA is needed to improve quantitative research within this field.

Donor selection for VCA still remains a largely unexplored field, mostly due to the limited experience in reconstructive transplantation, especially

when compared to solid organ transplantation. In a recent study analyzing the general acceptance of VCA among the public, respondents appeared to be significantly less willing to donate and/or receive a hand/upper extremity, lower extremity, abdominal wall, or face than they were for solid organs [16¹³]. Though a regional bias (urban area of a developing country) exists, interestingly 90% of respondents were willing to donate a kidney, while only 54% would donate hand/upper extremity and only 39% his/her face. The (public) attitude towards donation or acceptance of genital tissue has not been explored, but as this represents a highly identifying and intimate part of the human body, may be similar to that for the face. Many cultural, religious, socioeconomic and geographical factors may play a role in the attitude towards donation. The South African GUVCA team noted that offering the option of a phalloplasty in the donor after removal of the penis greatly changed the relatives' perception on penile donation and ultimately led to agreement of the donor's family [11¹⁴].

EXPECTED AND ANTICIPATED OUTCOMES

A successful outcome after penile transplantation will require an effective combination of immunological, surgical and psychosocial factors. GUVCA prognosis is based primarily on what we know from transplantation of the face and upper extremity, and from autologous penile replantation, yet neither of these fully encompasses the complexity of allotransplantation of different urogenital tissue types. Pre-clinical data on penile transplantation has been limited. In the majority of animal studies available in literature, heterotopic GUVCA is performed in rodent models and the native penis serves as a control [17–20] to evaluate the feasibility of the surgical procedure, penile perfusion, or the effect of immunosuppression. In a single other study, a canine large animal model was used for orthotopic penile transplantation [21¹⁵]. Twelve of 20 transplanted penises survived well. Eight penile grafts were removed after demonstrating paleness or signs of failure. Histopathology showed thrombosis, inflammatory cell infiltration, and tissue degradation in these cases. None of the available animal models effectively resemble the human phallus and its pathophysiology, including erectile function, contributing to the lack of preclinical knowledge surrounding GUVCA.

Cadaver studies have provided established and potential GUVCA teams with information on the great anatomical variations in critical penile structures

Table 1. Summary of penile transplantation cases and recommendations

	GUVCA	GUVCA	GUVCA	Cadaver study
	Cetrulo <i>et al.</i> , Boston, USA [7 ^{***}]	Van der Merwe <i>et al.</i> , Johannesburg, South Africa [3]	Hu <i>et al.</i> , Guangzhou, China [2]	Tuffaha <i>et al.</i> , Baltimore, USA [20]
Microsurgical anastomoses	Dorsal penile a. (single, right, to right femoral a. instead of native dorsal a.) Cavernosal a., bilateral Deep dorsal v. Dorsal penile n. Urethra	Dorsal penile a. (bilateral, to deep inferior epigastric a. instead of native dorsal a.) Deep dorsal v. Dorsal penile n. Urethra	Dorsal penile a., bilateral Superficial dorsal v. (?) Deep dorsal v. Dorsal penile n. Urethra	Recommended: Dorsal a., bilateral Cavernosal a., bilateral External pudendal a.
Conclusion vasculature	No external pudendal arterial anastomosis required (and single dorsal artery could be sufficient) Excellent flow to both penis and skin flap via cavernosal arteries and single dorsal artery	Not essential to perform anastomosis of the cavernosal arteries provided that good perfusion of the corpora cavernosa is attained by dorsal penile arterial supply. No external pudendal arterial anastomosis is required.	Insufficient vascular perfusion of the skin, with signs of epidermolysis and necrosis.	External pudendal arteries are required for penile shaft skin perfusion. Cavernosal a. may not be necessary (if dorsal a. anastomosed proximal to origin cavernosal a.)
Complications, including operative reinterventions	Hematoma POD2 Pubic skin eschar debridement POD13 Acute rejection (steroid-resistant, Banff I-III) POD28-32 Acute rejection (steroid-resistant, Banff III) POD325	Penile artery thrombus POD4 Hematoma Urethral fistula Infection (urinary catheter) (?) Phaohyphomycosis infection 8 months postoperatively	Epidermolysis and skin necrosis? Psychological rejection POD13, with removal of the allograft.	N/A

a., artery; GUVCA, genitourinary vascularized composite allotransplantation; n., nerve; N/A, not applicable; POD, postoperative day; v., vein.

[22,23[■]] and recommendations for vascular perfusion of a GUVCA. The patient-specific extent of tissue loss guides preoperative planning of the surgical technique for both allograft procurement and recipient site preparation for each individual case. Anatomic complexity can lead to unexpected intraoperative findings that are difficult to anticipate. In both the South African case and our case in Boston, recipient vasculature was compromised, demanding use of alternative vessels for microsurgical anastomosis [11[■]] (Table 1). Surgical flexibility and planning of alternative neurovascular solutions is important to ensure optimal perfusion and graft success.

Functional results have been highly promising, with excellent return of urinary function in both cases at 2–3 weeks, full return of erectile and sexual function in the South African case, and nocturnal penile tumescence with increasing quality and frequency in our recipient. However, in all three GUVCA cases performed worldwide, a comprehensive range of unplanned, yet anticipated, postoperative complications occurred (Table 1). Our patient required operative reintervention for hematoma evacuation on POD2, and pubic skin eschar debridement on POD13. Steroid-resistant rejection developed on POD 28 (Banff I), progressed by POD 32

(Banff III), and resolved after a repeat course of methylprednisolone and antithymocyte globulin. A second episode of rejection occurred on POD325 (Banff III), which was treated with steroids and antithymocyte globulin. The South African GUVCA recipient required surgical removal of a thrombus in one of the penile arteries at POD4. In addition, a wound hematoma and infection occurred postoperatively, which the team considers to be complicated by the trans-urethral catheter (and could have likely been prevented by a suprapubic catheter [11[■]]). In addition, at 8 months after the transplant, the patient developed a fungal infection (*Alternaria alternata*) on his foot, which was treated with surgery and a broad-spectrum topical antifungal agent. In light of this infection, the team questioned whether the recipient had been overly immunosuppressed. Tacrolimus dose was initially maintained at serum levels of 10–15 ng/ml, but after a decline in renal function blood levels, the serum levels were reduced to 5–10 ng/ml. Renal function improved after this decrease in calcineurin inhibitor (CNI), but the long-term impact on kidney function remains a concern for this young patient [24,25]. CNI levels in our MGH patient were targeted at 10–15 ng/ml, and at his one year anniversary of this transplant,

we transitioned him to low dose CNIs (3–6 ng/ml) with addition of low dose sirolimus (3–5 ng/ml) for preserving his native renal functions.

BARRIERS WE FACE IN DEVELOPING THE FIELD

Unique challenges are associated with a novel field like GUVCA, such as dealing with media attention and donor family education. Financial resources remain a big issue for highly experimental procedures like these, where insurance companies tend to cover only a part of the costs. To ensure clinical safety and effectiveness, strategies and detailed protocols have to be developed for significant intrahospital cooperation, between all departments, but also between multiple institutions. Multicenter qualitative research will be essential to study not only the long-term psychosocial effects and patient quality of life outcome, but also to recognize and minimize the profound risk profile that currently hinders a less selective application of GUVCA.

Acute and chronic rejection continues to be a serious risk for VCA, and the novelty of the immunological factors in GUVCA will be especially challenging for clinical follow-up of penile allograft recipients. Careful analysis of long-term results will have to guide future diagnosis and treatment of penile allograft rejection, as it is unclear if penile tissue types reject differently than those commonly part of VCAs. Penile shaft skin is hairless, highly elastic and lacks subcuticular fat, making it different than skin of the upper extremity and face. Skin is believed to be one of the earliest tissues to develop acute rejection, but since erectile function is a reflection of penile microvasculature, chronic rejection might be displayed as erectile dysfunction in the setting of penile transplantation. Sopko *et al.* [26²²] recently published an ex-vivo study evaluating a novel model of human cavernosal tissue (recipient) together with peripheral blood mononuclear cells (donor) in order to mimic the clinical effects of rejection and immunosuppression on erectile tissue. Rejection was shown to impair cavernous tissue physiology, decrease smooth muscle relaxation, and was associated with cellular infiltration and apoptosis. Cyclosporin A prevented rejection, but led to impaired corporal smooth muscle relaxation, while tacrolimus did not show this effect.

CONCLUSION

With only three cases done worldwide, genitourinary vascularized composite allotransplantation remains in an early developmental state. Transplant

and microsurgical experts should cautiously explore a variety of technical, immunological, ethical, and psychosocial considerations before implementation of a GUVCA program. Detailed knowledge on the risk profile and benefits is required for conversion of GUVCA to a nonexperimental treatment option. Collaborative guidelines, protocols, and a standardized evaluation model should be implemented in multiple centers to ensure clinical applicability despite the ethical reservations associated with this challenging yet life-enhancing procedure.

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Conflicts of interest

The authors report no conflicts of interest.

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- of special interest
- of outstanding interest

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