

Penile allotransplantation for total phallic loss due to ritual circumcision: Proof of concept



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Penile allotransplantation for total phallic loss due to ritual circumcision: Proof of concept

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Presented in fulfillment of the requirements for the degree of Doctor of Philosophy
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DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes **five** original papers published in peer-reviewed journals or books and **four** unpublished publications. I am the first author of all **nine** publications and contributed 60 -100% of all the papers. The development and writing of the papers (published and unpublished) were the principal responsibility of myself.

Signed by André van der Merwe

Date: 9 August 2020

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Lastly and mostly, I thank my three lovely boys, Henry (17), Theuns (14), and André Jnr. (12), whose loveliness transcends all, for accompanying me on this challenging journey. I dedicate this dissertation to them.

SUMMARY

Ritual circumcision is an important tradition practiced by many African cultures in South Africa. These circumcisions occasionally result in severe penile mutilations, and many men are rendered aphallic as a result. Phalloplasty represents conventional treatment for these cases. However, this type of surgery has many challenges, which make it an undesirable treatment option, particularly in low- to middle-income settings, such as South Africa.

Therefore, we considered alternatives to phalloplasty that were technically feasible and cost-effective. Penile allotransplantation was largely unexplored as a therapeutic option at the inception of the study in 2011, and it was uncertain if a penis transplant would restore all the functions of a normal penis. We undertook a proof of concept investigation and explored the feasibility of penile transplantation in our resource-constrained hospital setting.

This is a prospective mixed-methods observational study. Following Human Research Ethics Committee approval, ritual circumcision related aphallic patients attending the Urology Clinic at Tygerberg Academic Hospital were invited to participate. Informed consent was obtained following the intense briefing of candidates over several visits. Various blood tests were conducted, after which selected patients were waitlisted.

The first donor became available in December 2014, and the most suitable recipient was selected based on blood group matching and a negative T-cell cross match. The donor penis was retrieved and transplanted by using the same basic principles of vascularised free flap surgery. Intense immunotherapy was initiated. Outcomes were recorded in terms of recovery from surgery, sexual function, standing to urinate, and general psychological recovery. In the first case-report at 24 months postoperatively, we used standardised pre-and post-surgery Short-Form (SF-36) health questionnaires as well as the International Index of Erectile Function (IIEF) scores to document erectile function outcomes.

After that, we used lessons learned from the first case to construct a preliminary guidance manuscript on penile transplantation. We performed a second penile transplant case with 40 months follow-up using patient-reported outcomes as a

measure of success in terms of erectile function, sexual satisfaction, and general well-being. We reviewed the ethics around penile transplantation in the context of our experience gained performing two penile transplantations and the societal and academic responses to these cases. Using a phenomenological approach, we conducted four in-depth interviews and performed a thematic analysis to describe study participants' experiences of living with another person's penis. Finally, we investigated the current state of penile transplantation by a review of the English literature using available primary databases. Additionally, we published two book chapters on penile transplantation and a manuscript of rebuttal to an argument against penile transplantation. These are attached as addenda to the current thesis.

Patients with penile loss are suffering severely. Their self-image, as well as relationships, are destroyed with no effective treatment available to them. Penile transplantation offers hope for the restoration of their broken body image and relationships. Also, this study may pave the way for penile- or total genital transplantation in trans males.



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2 August 2019

Dr Nicola Barsdorf
HREC
Tygerberg Campus

Dear Dr Barsdorf

APPLICATION ACCEPTED BY THE REVIEW COMMITTEE: PHD IN UROLOGY BY PROF ANDRÉ VAN DER MERWE (11066431)

Please be informed that the candidate Prof André van der Merwe's application has been approved by the Review Committee as indicated by the supporting document. The HREC representatives were Marilize Burger (HREC 2) and Elize Archer (HREC 2).

Kind regards

J. A. Chabilall

Jyothi Chabilall

Head: Doctoral Office



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Approval Notice

New Application

24/10/2019

Project ID :11142

HREC Reference No: S19/08/169

Project Title: Penile allotransplantation for total phallic loss due to ritual circumcision - proof of concept.

Dear Prof Andre Van der Merwe,

The **Response to Modifications** received on 23/10/2019 12:26 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 24/10/2019 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Date: 24 October 2019

Protocol Expiry Date: 23 October 2020

Please remember to use your Project ID [**11142**] and Ethics Reference Number [**S19/08/169**] on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see [Forms and Instructions](#) on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: <https://www.westerncape.gov.za/general-publication/health-research-approval-process>. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: [Forms and Instructions](#) on our HREC website <https://applyethics.sun.ac.za/ProjectView/Index/11142>

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372

Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:

IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the [World Medical Association \(2013\). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects](#); the [South African Department of Health \(2006\). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa \(2nd edition\)](#); as well as the [Department of Health \(2015\). Ethics in Health Research: Principles, Processes and Structures \(2nd edition\)](#).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

GENERAL INTRODUCTION

Ritual circumcision and possible complications

Complications due to ritual circumcision have plagued young South African men for many years. [1-4] These complications are mostly phallic mutilations and even deaths from dehydration, and sepsis. This rite of passage is shrouded in secrecy, and geographical variations in the conduct likely exist. It is also prevalent in Eastern Africa. The yearly frequency of quoted fatalities, and the approximate number of 250 phallic mutilations or losses, is probably an underestimate as these men are not supposed to seek Western help after ritual circumcision failures. [5]

Ritual circumcision is seen as a watershed event in the lives of mainly young isiXhosa tribal men in South Africa. During the four to six-week ritual of the traditional initiation process, they receive valuable information on adult behaviour and tribal coherence. At the start of these circumcision 'bush' camps, they undergo circumcision by an experienced circumciser. Appointed carers achieve haemostasis by wrapping herbal leaves and a buckskin bandage tightly around the circumcised penis. The carers take responsibility for the initiate for the length of the ritual. [6] The circumcisers and carers are, however, often inexperienced, intoxicated, and abusive. [7;8]

When the buckskin is wrapped too tightly around the penis, it impedes blood flow, causing varying degrees of gangrene; [2;6] the skin or distal part of the penis may become ischaemic and necrotic (Figure 1A); however, at times the entire pendulous penis may become gangrenous as the bandage covers the whole penis (Figure 1B). The defect, once healed, is then flush with the abdomen (Figure 1C). Initiates are water restricted to minimise urination, and the restrictive bandage makes urination difficult. By not drinking, the chances of acute retention are reduced. As many of these ritual circumcision camps occur in the African summertime, dehydration coupled with infected gangrenous tissue cause septicemia, acute kidney injury, and death. [1;9].



Figure 1: Complications of ritual circumcision. A) Penile necrosis may be incomplete; B) Complete pendulous penile necrosis; C) Penile necrosis defect after a period of recovery.

Initiates are not allowed to seek Western medical assistance. If they do, they may be physically harmed or even killed by cultural purists. [4;10] Men who 'failed the custom' are seen as weaklings, boys, even 'dogs' and will never obtain any status or leadership positions in the community. [3;8]

Once recovered, they live in fear of being discovered. They may suddenly leave their employment if colleagues become suspicious of their failure. It is acceptable for the tribal members to insist on other tribe members to demonstrate their genitalia to prove their status. The effect is that these men who have survived a complicated circumcision withdraw socially; they are ostracised and become the least respected members of their society. They have no support from their families either as they are believed to bring shame onto the family. Suicide is the most dignified way to escape this situation. Three of the waitlisted men described how suicide is usually planned. [11] The depressed young man will buy food and poison and return to the area where he failed his tribe and family - never to return. Due to political complexity, the South African Government has not yet intervened. Ncayiyana remarks on the 'astonishing indifference' of the government that appears to turn a blind eye to the dire situation. [12]

At our institution, we frequently encounter hospitalised young men presenting with gangrene of the penis. They are often very desperately ill, requiring intubation and ventilation. Once recovered, they are referred to the plastic surgery waitlist for phalloplasty of which only two or three are done yearly. Due to the technical challenges

associated with this procedure, phalloplasty takes about 7 - 8 hours of operating time to complete. Donor tissue is sourced from the forearm of the patient, leaving a visible scar, and sensitive skin due to the covering skin graft. This defect may give a clue to the failed ritual and may also impede manual labour. The phalloplasty free flap may also shrink post-operatively and cannot receive a prosthesis, or the prostheses may extrude. The phalloplasty may have urethral complications preventing urination in the standing position. [13;14] Relatively few of these procedures have been done at our institution because of capital cost considerations.

We wanted to find an alternative to phalloplasty for our patients. As we were also performing renal transplantation, we considered penile transplantation. We considered the following ten parameters that would prove the concept of penile transplantation feasible in our setting.

1. Our transplant team, experienced in all aspects of renal transplants, should be able to learn and extrapolate from existing knowledge the skills needed to perform penile transplantation, which is a type of vascular composite allotransplantation (VCA).
2. While urologists on the team were versed in microsurgery, the assistance of plastic surgeons experienced in vascularised free flap surgery would be needed to increase the chances of free flap survival.
3. We considered ethical matters vital to the success of the project; therefore, we would need a team ethicist to guide the study and build bio-ethical capacity.
4. We acknowledged the psychological impact of losing the penis and the need to include a dedicated hospital psychologist on the team.
5. Government approval to transplant and transport a new type of tissue, the penis, was required.
6. We estimated that penile transplantation should not be more costly than renal transplantation based on the healthy individual, lack of renal replacement therapy, the use of generic immunosuppressive medication. The prolonged operative time phalloplasty required and capital cost saved by not inserting a penile prosthesis would add to our argument. Based on this, the hospital would need to agree to sponsor the project as a 'clinical event' as sponsorship application failed.

7. We would need to obtain Human Research Ethics Committee (HREC) approval at Stellenbosch University and the Western Cape Department of Health.
8. The penis transplant should restore urinary function to allow standing urination.
9. The penis transplant should restore sexual function.
10. The penis transplant should lead to improved psychological functioning.

The research question, aims, and objectives

Based on these considerations, our final research question was:

Is penile transplantation in men who suffered a loss of penis after ritual circumcision feasible, and can this procedure improve the physiological functioning and lived experience of the recipient?

The concomitant aim of our study was:

To determine the feasibility of penile transplantation in men who suffered a loss of penis after ritual circumcision, and whether this procedure can improve the physiological functioning and lived experience of the recipient.

To achieve this aim, the following activities were performed:

1. Two penile transplantations (Chapters 1 and 3).
2. Following the first procedure, we constructed a preliminary guidance manuscript on penile transplant (Chapter 2).
3. We reviewed the ethics around penile transplantation in the context of our experience gained performing two penile transplantations. (Chapter 4).
4. Using a phenomenological approach, we conducted four in-depth interviews and performed a thematic analysis to describe study participants' experiences of living with another person's penis (Chapter 5).
5. Finally, we investigated the current state of penile transplantation by a review of the English literature using available primary databases (Chapter 6).

In addition to these chapters, we published two book chapters on penile transplantation and a manuscript of rebuttal to an argument against penile transplantation.

These are attached as addenda to the current thesis:

Addendum A - Book chapter: Van der Merwe A, Zarrabi AD. *Penile transplantation: The last frontier in penile reconstruction*. In Martins FE, Kulkarni SB, Kohler TS, editors. *Textbook of Genitourinary reconstruction*. Springer, 2020, pp. 795-804. [15]

Addendum B - Book chapter: Van der Merwe A. *The role of penile transplantation after penis cancer surgery*. In Martins F, Djordjevic M, editors. *Penile Cancer - Challenges and Controversies*. Nova Medicine and Health, 2020, pp. 209-219. [16]

Addendum C - Journal publication (A rebuttal published in response to an argument against penile transplantation in the Journal of Medical Ethics): Van der Merwe A. *In response to an argument against penile transplantation*. *J Med Ethics* 2020; 46:63-64. [17]

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- (17) van der Merwe A. In response to an argument against penile transplantation. J Med Ethics 2020; 46:63-64.

CHAPTER 1

Penile allotransplantation for penis amputation following ritual circumcision: A case report with 24 months of follow-up

This chapter consists of a published manuscript in which we discuss the first penile transplant that we attempted in 2014. This manuscript was published in The Lancet, as follows:

Van der Merwe A, Graewe F, Zuhlke A, Barsdorf NW, Zarrabi AD, Viljoen JT, Ackermann H, Spies PV, Opondo D, Al-Qaoud T, Bezuidenhout K, Nel JD, Bailey B, Moosa MR. *Penile allotransplantation for penis amputation following ritual circumcision: a case report with 24 months of follow-up. Lancet 2017; 390:1038-1047.*

Following the manuscript, we have included an update that describes the current status (as of 20 July 2020) of the recipient.

Penile allotransplantation for penis amputation following ritual circumcision: a case report with 24 months of follow-up



André van der Merwe, Frank Graewe, Alexander Zühlke, Nicola W Barsdorf, Amir D Zarrabi, Jeremy T Viljoen, Hilgard Ackermann, Pieter V Spies, Dedan Opondo, Talal Al-Qaoud, Karla Bezuidenhout, Johan D Nel, Bertha Bailey, M Rafique Moosa

Summary

Introduction Ritual circumcision complicated by gangrene is a leading cause of penile loss in young men in South Africa. This deeply rooted cultural tradition is unlikely to be abolished. Conventional reconstructive techniques using free vascularised tissue flaps with penile implants are undesirable in this often socioeconomically challenged group because donor site morbidity can hinder manual labour and vigorous sexual activity might lead to penile implant extrusion. The psychosociological effects of penile loss in a young man are devastating and replacing it with the same organ is likely to produce the maximum benefit.

Methods We first performed a cadaver-to-cadaver penile transplantation as preparation. After approval from the Human Research Ethics Committee was obtained, we recruited potential recipients. We screened the potential participants for both physical and psychological characteristics, including penile stump length, and emotional suitability for the procedure. A suitable donor became available and the penis was harvested. We surgically prepared the penile stump of the recipient and attached the penile graft. Immunosuppression treatment with antithymocyte globulin, methylprednisolone, tacrolimus, mycophenolate mofetil, and prednisone were commenced. Tadalafil at 5 mg once per day was commenced after 1 week as penile rehabilitation and was continued for 3 months. We collected on quality-of-life scores (Short Form 36 version 2 [SF-36v2] questionnaires) before surgery and during follow-up and measured erectile function (International Index for Erectile Function [IIEF] score) and urine flow rates at 24 months post transplant.

Findings The warm ischaemia time for the graft after removal was 4 min and the cold ischaemia time was 16 h. The surgery lasted 9 h. An arterial thrombus required urgent revision 8 h after the operation. On post operative day 6, an infected haematoma and an area of proximal skin necrosis were surgically treated. The recipient was discharged after 1 month and first reported satisfactory sexual intercourse 1 week later (despite advice to the contrary). The recipient reported regular sexual intercourse from 3 months after the operation. An episode of acute kidney injury at 7 months was reversed by reducing the tacrolimus dose to 14 mg twice per day. At 8 months after surgery, the patient had a skin infection with phaeohyphomycosis due to *Alternaria alternata*, which we treated with topical antifungal medication. Quality-of-life scores improved substantially after the operation (SF-36v2 mental health scores improved from 25 preoperatively, to 57 at 6 months and 46 at 24 months post transplant; physical health scores improved from 37 at baseline to 60 at 6 months and 59 at 24 months post-transplant). At 24 months, measured maximum urine flow rate (16.3 mL/s from a volume voided of 109 mL) and IIEF score (overall satisfaction score of 8 from a maximum of 10) were normal, showing normal voiding and erectile function, respectively.

Interpretation Penile transplantation restored normal physiological functions in this transplant recipient without major complications in the first 24 months.

Funding Department of Health, Western Cape Government.

Introduction

Penile loss and injury can have various causes.¹⁻⁴ A distressing number of healthy young men in South Africa are rendered aphallic because of complications arising from ritual circumcisions.^{5,6} Ritual circumcision is deeply rooted in cultural practice in South Africa, especially among the Xhosa-speaking people of the Eastern Cape. Circumcision is an integral part of a larger initiation ritual, which is considered a rite of passage to manhood. The initiation ritual serves an educational function, preparing older adolescents for the challenges and responsibilities of adulthood. The ritual is generally an eagerly anticipated event in a young man's life, symbolising his transition to manhood; failure to comply

results in social stigmatisation.⁷ Groups of young Xhosa men voluntarily enter this month-long camp, colloquially referred to as "going to the bush", for a period of seclusion. During the ritual process, the circumcisionist removes the foreskin with an assegai (traditional spear). A haemostatic bandage of a strip of buckskin or cloth and herbal leaves is wrapped tightly around the full length of the pendulous penis encroaching the pubic skin. The initiates are then confined to a hut for the first 8 days and the consumption of certain foods and drinks is restricted. During the seclusion period the initiates receive sexual and cultural counselling that prepares them for the responsibilities of adulthood and family life.¹

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Research in context**Evidence before this study**

We searched PubMed and MEDLINE up to July, 2016, using the MeSH terms penile “transplantation”, “penis allotransplantation”, “penile gangrene”, “phalloplasty”, “ritual circumcision”, “botched circumcision”, “SF 36” AND “penis/penile”, “gender reassignment”. In South Africa many young men are rendered aphallic as a very serious complication of traditional circumcisions. To date these men who have suffered penile loss have not been optimally managed, thus depriving them of dignity and satisfaction in life. Although prostheses and phalloplasties are available, therapeutic approaches are expensive and fraught with complications. We explored the option of a penile allotransplant as a definitive procedure. The first penile allotransplant was done Guangzhou, China, in 2005. The allograft was removed 2 weeks later because of psychological rejection by the donor’s wife. In this study, we report the second penile allotransplant, which was done in Cape Town, South Africa. A subsequent transplant was done in Boston, USA, in 2016 and we successfully performed our second allotransplant on April 21, 2017.

Added value of this report

This is the first report of a penis transplant that has resulted in restoration of all physiological functions of the penis. The main

value of our report is that of proof of concept, removing the doubt that normal erections could be achieved with an allotransplanted organ and challenges reports of potential major skin necrosis after penile transplantation. An important aspect of the process is the careful screening and selection of the recipients, as well as consideration of the ethical issues pertaining to the procedure. The benefit of a successful transplant must be weighed against the inevitable consequences of lifelong immunosuppression.

Implications of all the available evidence

There are many circumstances under which penile loss occurs and the knowledge that penile allotransplantation is now a feasible option can give hope to affected patients.

Vascularised composite allotransplantation is still novel and much about this form of transplantation remains uncertain.

We believe that our experience will help to progressively improve the way in which vascularised composite

allotransplantation is managed. Penile allotransplants present unique sociocultural and ethical challenges, and the success of the procedure should stimulate societal discourse on dealing with these issues.

Current ritual circumcision practices in South Africa have raised serious health concerns. Complications of the procedure result in severe penile mutilation or varying degrees of penile amputation in roughly 250 young men per year⁵ and mortality is unacceptably high (9%) among those admitted to hospital.⁸ Because of the secrecy of the process, reliable data on complications are scarce.^{9,10} Ritual circumcision is typically done in a non-clinical setting by a traditional circumciser with minimal, if any, formal clinical training. In addition to the surgical risks, if the haemostatic bandage is applied excessively tightly, the penile skin or the whole pendulous penis can undergo necrosis. Furthermore, the initiates are discouraged from fluid intake in the days after the circumcision in an attempt to reduce urine production and voiding, and thus prevent acute urine retention. The resulting dehydration predisposes initiates to thrombosis of the penile blood vessels, increasing the risk of penile necrosis. The constrictive bandage can cause necrosis of the pendulous penis at various levels depending on the extent of pressure applied. Loss of the penis deprives the young man of the ability to urinate standing, to enjoy normal sexual intercourse, or to impregnate a female partner. Of even greater concern, is that infection is common and subsequent septicaemia causes an estimated 100 deaths each year. Complications are often not reported to health authorities because this “shames the custom” and might be punished with physical violence by cultural purists.^{5,6,11,12}

Conventional reconstructive techniques, including free vascularised tissue transfer, are imperfect substitutes for a normal penis. Common complications include flap atrophy or necrosis, urethral strictures, extrusion of the prosthesis, and cosmetically unacceptable hair growth.^{13,14} The radial forearm (fasciocutaneous) flap currently used in our practice can impair functional capacity in patients who rely heavily on manual labour to earn a living. The cost of penile implants after free-flap reconstructive surgery, combined with the potentially high extrusion rate in a young sexually active population, makes this option less desirable in the resource-constrained context of South Africa. The high risk of complications, general scarcity of reconstructive expertise, and high cost of a suitable prosthesis created the need for a more suitable alternative; this alternative had to have few complications, be cosmetically acceptable, restore normal sexual function, and permit normal urination. The first attempt at penile allograft transplantation was reported from Guangzhou, China, in 2006. The surgery was technically successful; the penis was warmed post operatively with an infra-red lamp and had superficial skin necrosis on histology with viable corpora cavernosa and corpus spongiosum. The transplanted penis was removed 14 days after the surgery at the request of the recipient’s partner.¹⁵ The current report describes the second penis transplant; the third was done in Boston, MA, USA, in 2016. We can report that we did a subsequent penis transplant on April 21, 2017, which was our second case.

The notion that to be ethical, research must be socially valuable is widely accepted in medical ethics.¹⁶ Research that imposes risks and burdens to participants is only justified when it has sufficient social value. The local social value of penile transplantation in South Africa is shown by the relatively large number of young men rendered aphallic following complications of ritual circumcision.⁵ Alternative forms of penile replacements were not considered suitable in this setting. Although not life saving, penile transplantation can be significantly life enhancing, especially for the post-adolescent young men most affected by penile loss, at a stage in their life where they have not yet had the opportunity to partner or father children.¹⁷

In view of the large number of healthy young men rendered aphallic each year, and the shortage of feasible or affordable reconstructive alternatives for our local population, we investigated the feasibility of penile transplantation within the resource-constrained public health sector in South Africa. We report here the first functionally successful penis allotransplant procedure with 24 months of follow-up.

Methods

Setting

Our renal transplant unit, which also serves as a composite tissue transplant unit, is situated in Tygerberg Academic Hospital, a tertiary academic, public-sector hospital in Cape Town, South Africa. The renal transplant unit is serviced by a team of nephrologists and urologists. The urologists provide support in terms of vascular access and are responsible for all kidney transplants. The nephrologists are responsible for the postoperative care of patients receiving renal transplants, including immunosuppression. The urology team also routinely manages complications from ritual circumcision and, together with the nephrologists, were therefore well placed to perform the penile transplant. Our proof-of-concept study fits with stage 1 ("Idea") of the IDEAL framework for new surgical procedures.¹⁸

Preparation and patient selection

Before attempting the penile transplant with a live patient, we did a cadaver-to-cadaver penile transplant to familiarise ourselves with the anatomy and potential sources of blood supply to match the diameter of penile graft neurovasculature. We then identified young men with complete penile amputations resulting from ritual circumcision. Some patients were referred to us from other hospitals for management of complications arising from ritual circumcisions, because we are the tertiary centre serving the affected region. Men aged 18 years or older with total or partial penile loss as a complication of ritual circumcision, who were willing to provide written, informed consent were included in the study and placed on a waiting list similar to that for potential kidney recipients. We screened all potential participants

physically and psychologically. We assessed 16 patients, of whom 12 were placed on the waiting list; of the four patients excluded, two had residual phalluses that were deemed adequate for all penile functions, making risk-benefit ratios unfavourable, and two had psychiatric diseases that precluded safe transplantation. Those men deemed unsuitable for transplantation were referred for assistance to a plastic surgeon and a psychologist as appropriate. Suitable participants underwent tissue typing, blood grouping, and screens for hepatitis B virus, cytomegalovirus, and HIV. In our renal transplantation practice, we do not routinely screen for Epstein-Barr virus or any of the other viruses associated with malignancies; we extrapolated this practice to the management of the penile transplantation. Patients with HIV or hepatitis B virus infections who failed to develop immunity to the hepatitis B virus were excluded. Other exclusion criteria were any active bacterial infection (including tuberculosis), any evidence of psychiatric disease or history of substance abuse; urological criteria for exclusion were penis remnant sufficient for vaginal penetration or for urination standing. We did not do imaging studies of the recipient vasculature because we felt that these would be of little benefit in planning the surgery and add unnecessary expense.

The transplant recipient was chosen from a waiting list of 12 candidates on the basis of immunological parameters that would minimise risk and complications of long-term immunosuppression and on psychological status. He was selected as the first research participant over other potential recipients based on his lower risk profile. This patient was a 21-year-old man who had been rendered aphallic 3 years previous to the transplantation following a ritual circumcision complicated by gangrene of the pendulous penis, depriving him of all the normal functions of a penis. The loss left him psychologically and emotionally bereft. He was fully assessed for penis allotransplantation and deemed to be a suitable candidate.

Once the recipient had been selected, we administered the Medical Outcomes Study Questionnaire Short Form 36 Health Survey version 2 (SF-36v2) preoperatively and at 6 months and 24 months after surgery; the average score for each section in the population in the USA is 50. The whole form was administered to allow electronic validation by Optum Health software. The International Index for Erectile Function (IIEF) score was recorded at 24 months. Stellenbosch University's Health Research Ethics Committee approved this project in 2011 (N11/07/243).

Ethics

The ethical issues surrounding penile transplantation are complex, and similar in some respects to those inherent to facial transplantation.¹⁹⁻²⁵ The full range of ethical issues will be discussed in detail in a separate publication, but we briefly address selected pertinent ethical considerations here.

For SF-36v2 see <https://www.optum.com/optum-outcomes/what-we-do/health-surveys/sf-36v2-health-survey.html>



Figure 1: Injection of ice-cold Custodial HTK solution into the corpora cavernosa

We identified and minimised the potential risks to individual participants to move towards a favourable risk-benefit ratio. In addition to the physical risks of long-term immunosuppression after transplantation, these patients face potential risks of social and psychological harm. The prevailing South African sociocultural environment requires that this experimental treatment be managed with extreme sensitivity. We considered protecting the privacy of our transplant recipient to be paramount to preventing any potential stigmatisation or discrimination. Another important consideration was adherence to treatment. Emerging adulthood, defined as 18–25 years is a high risk period for non-adherence to immunosuppression regimens in renal transplantation. The reason for this behaviour is postulated to be that the brain continues to mature until the age of 25 years.^{26,27} Additionally, the psychological effect of penile transplantation cannot be underestimated and could induce psychosis or renunciation of the organ.²⁸ Extrapolating from this possibility, we took particular care in selecting candidates for the waiting list who were proven to be compliant with treatment and clinic attendance and considered physically and psychologically suitable for penile transplantation.

The participant selected to receive the transplant was counselled on the potential risks and benefits of the procedure for 2 years before transplantation. During this period, we addressed ethical issues surrounding penile transplantation including the risk of therapeutic misconception, innovative alliance between the eager patient and surgeon, and selective hearing by the participant not attending to potential side-effects of immunosuppression.^{22,29}

Procedures

A suitable donor (36 years old, brain-dead, beating heart) became available on Dec 10, 2014, and consent for multi-organ recovery was obtained from the donor's family, including the heart, liver, kidneys, and penis, with the recovery occurring in that order. The donor and recipient shared blood group A+ and the T-cell cross-match was negative. The recipient only shared HLA-B7 with the donor (donor: HLA-A1-32, HLA-B7-44, and HLA-DR7-16; recipient: HLA-A24-24, HLA-B7-7, and HLA-DR 3-15). The recipient had 8% HLA class I antibodies, but no HLA class II antibodies. The HLA class I antibody was specific for HLA-B35. No donor-specific antibodies were detected in the recipient's serum. Both donor and recipient tested negative for the HIV, hepatitis B virus, and hepatitis C virus. The donor and recipient were both positive for cytomegalovirus immunoglobulin G.

The donor penis was harvested at the level of the inferior pubic rami. The cold ischaemia time was 16 h. The prolonged cold ischaemia was enforced by our need to prioritise the kidney transplant done by the same team, as well as other logistical issues, including competition for access to operating theatres in a busy academic hospital. The dorsal penile neurovascular structures were identified and dissected as far proximal as possible before the penis was transected. The warm ischaemic time was 4 min. The penis was cooled by irrigating ice cold Custodial HTK solution (Essential Pharmaceuticals, Ewing, NJ, USA) directly into the corpora cavernosa; we resorted to this technique when we found that intra-arterial perfusion via the dorsal penile arteries was not possible because of excessive cannula size (figure 1). We prepared the corpora, nerve, and vascular structures on the bench. We fashioned an abdominal skin flap phallus to resemble a penis for the donor; this procedure took about 30 min to complete and was done for cosmetic reasons as agreed beforehand with the donor's family and was crucial in obtaining their consent.

The penile stump of the anaesthetised recipient was prepared by excising the distal approximately 0.5 cm of the corpora cavernosa and isolating the urethra and spongiosal stump (figure 2). We found that the dorsal penile vascular structures of the recipient had been obliterated by the ineffective and ischaemic processes that initially led to the penile loss. The left inferior epigastric artery was therefore mobilised via a paramedian skin incision, distally transected once adequate length and a matching diameter to the donor vessels was achieved, and re-routed subcutaneously. The inferior epigastric artery was anastomosed to the right dorsal penile artery under microscope magnification by use of a 9-0 nylon suture. The contralateral dorsal penile artery was similarly anastomosed to the left superficial external pudendal artery (figure 3). We used a 2 mm GEM Microvascular Anastomotic COUPLER ring (Synovis Micro Companies Alliance, Birmingham, AL, USA) for the anastomosis of the deep dorsal vein of the penis to

one of the deep inferior epigastric veins. The vascular clamps were released before we made the cavernosal and spongiosal anastomoses. On release of the clamps the penis perfused well with immediate pinkening of the glans penis and with blood flowing freely from the corporeal and spongiosal tissue. Both dorsal nerves were repaired under loupe magnification with a 9-0 nylon epineural suture. The urethra was spatulated and anastomosed with interrupted 3-0 polyglycolic acid sutures. The tunica albuginea of the cavernosal bodies and urethra were sutured in a watertight fashion with interrupted 2-0 polyglycolic acid sutures (figure 4). Skin was closed subcutaneously with 4-0 poliglecaprone sutures.

The patient made an uncomplicated recovery from anaesthesia and was subsequently transferred to the Renal Transplant Intensive Care Unit. Pain was treated with intravenous morphine sulphate at 5–10 mg every 6–8 h as required. Prophylactic anticoagulation was commenced with unfractionated heparin 5000 IU twice per day subcutaneously for 3 weeks. Immunosuppression was initiated postoperatively with induction therapy consisting of intravenous antithymocyte globulin (ATG, Fresenius Kabi, Bad Homburg vor der Höhe, Germany) at 100 mg per day for 10 days (figure 5). The patient received intravenous methylprednisolone at 500 mg preoperatively and at 250 mg per day for 3 days postoperatively, followed by oral prednisone at 30 mg per day. The dose of prednisone was maintained for almost 3 months, then tapered to 10 mg per day over 8 weeks. The recipient was also commenced on tacrolimus at 5 mg twice per day on the basis of his bodyweight. The dose of tacrolimus was monitored and adjusted to maintain serum residual levels 10–15 ng/mL. Mycophenolate mofetil was commenced at 500 mg twice per day for 3 days, then increased to 1 g twice per day. Additionally, the patient received 160 mg trimethoprim and 800 mg sulfamethoxazole per day as prophylaxis against *Pneumocystis jirovecii* and isoniazid at 300 mg per day as prophylaxis against tuberculosis. Both agents were prescribed for 1 year. Full blood count and serum urea and creatinine were monitored daily for the first 10 days. The serum glucose and creatinine concentrations of the recipient were also monitored weekly or more frequently in the first month after discharge, and monthly thereafter; then 3 monthly after 6 months or as determined by the caring physician. Tadalafil at 5 mg once per day was commenced 1 week after the operation as penile rehabilitation and was continued for 3 months. The use of tadalafil was extrapolated from its use in penile rehabilitation after surgery for prostate cancer.³⁰ We monitored acute rejection of the graft by visual examination of the skin, which is the most immunogenic component of the allotransplant. Any clinical signs of rejection would have triggered a skin biopsy. We opted not to use routine skin biopsies of the graft to detect acute rejection, as done in vascularised composite allotransplants, because of concerns about infection in a



Figure 2: Penile stump before penile transplantation

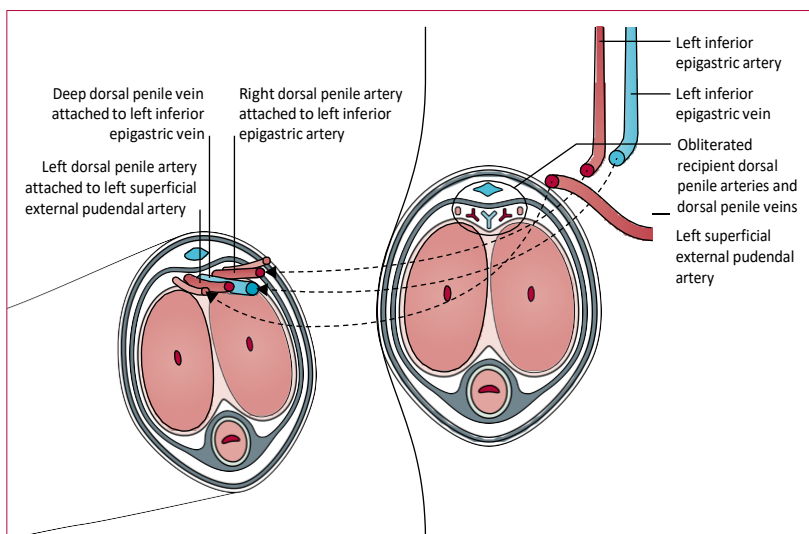


Figure 3: Summary of penile transplant surgery

sexually active, immunosuppressed young man and the limited skin area available for biopsy. We did not use a satellite donor skin transplant because of the relatively poor predictive value of this technique for diagnosing rejection in the actual graft;³¹ this approach is often taken in vascularised composite allotransplants because it removes the need to biopsy the vascularised composite allotransplant itself to diagnose rejection.^{31,32}

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The surgery and immunosuppression were funded as a one-off concession with no further conditions,

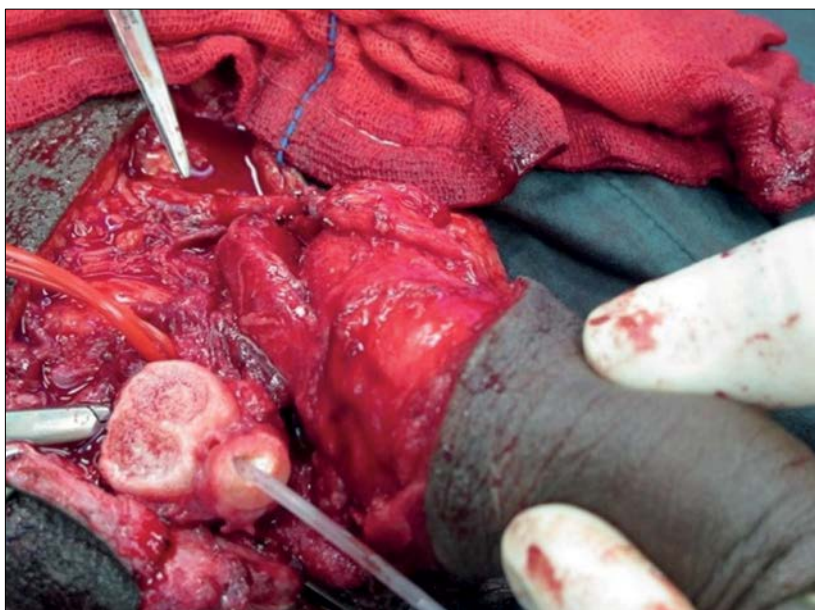


Figure 4: Completed vascular anastomosis prior to corporeal and urethral anastomoses

and future cases would require motivation on a case-by-case basis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The recipient was observed postoperatively in the Post operative Acute Care Unit for 24 h and then transferred to the Renal Transplant Intensive Care Unit to be cared for by experienced transplant nursing staff. The arterial anastomosis to the external superficial pudendal artery required urgent revision 8 h after surgery because of thrombosis of the right dorsal penile artery anastomosis. This thrombosis was possibly caused by a slight decline in blood pressure following opioid administration. Urgent thrombectomy and successful reanastomosis were performed; thereafter blood pressure was carefully maintained and the dosing interval of heparin was increased to three times per day. Thrombosis did not recur.

The patient expressed delight on day 3 at the first sight of the transplanted organ when the dressings were removed for the first time, declaring "I want to see my penis". Because of an infected haematoma and skin oedema, combined with a small amount of proximal skin necrosis, the patient was returned to theatre on day 6 for evacuation of the haematoma and minor skin debridement; a suprapubic catheter was placed to divert the urine flow away from the urethra and to reduce the risk of infection. The suprapubic catheter became obstructed by a blood clot on day 8 causing the patient to pass urine through the transplanted urethra. This resulted in disruption of the urethral anastomosis and the development of a urethrocutaneous fistula. The fistula

failed to close spontaneously and required surgical repair at 3 months. Throughout the early and late postoperative periods the penis remained warm and well perfused, as evidenced by the pink colour of the skin and glans penis. Penile rehabilitation consisted of maintenance tadalafil for 3 months after surgery. Erections were first reported by the recipient 3 weeks after surgery and he confirmed this with photographs he had taken himself. The recipient reported satisfactory penetrative sexual intercourse at 5 weeks after the operation, despite our advice to abstain for at least 3 months; on examination at this time however there were no signs of corporeal anastomotic leak or haematoma of the penis.

Up to 3 months after the transplant, all erections had been self-reported, but we witnessed a normal erection on the operating table on induction of anaesthesia at the time of his urethrocutaneous fistula repair. At the time of this operation the patient was still receiving tadalafil penile rehabilitation treatment, but it was discontinued shortly thereafter. The patient was carefully monitored and the immunosuppressive medication was well tolerated throughout, with no clinical signs of rejection.

The recipient was diagnosed with acne soon after commencement of steroids but this resolved by 7 months as the dose of the steroids was progressively tapered. At 5 months, the patient was noted to have elevated blood pressure, which resolved when the prednisone dose was reduced. At 8 months, he complained of a painful right foot and knee; on examination he was found to have an infected supra-patellar bursa. This was drained and a biopsy of the foot lesion confirmed infection with phaeohyphomycosis due to *Alternaria alternata*. Fungal blood cultures were negative and the patient remained systemically well. Treatment was commenced with topical broad spectrum clotrimazole antifungal cream, leading to the slow but steady resolution of the lesion.

24 months after the operation, the patient is doing well with no episodes of rejection. He reports regular satisfactory sexual intercourse in a stable relationship with normal ejaculation and orgasm. He accepted the penis as his own, despite a small tuft of donor pubic hair growing at the dorsal base of the graft. 6 months after the transplant, the patient reported that his partner was about 3 months pregnant; sadly, she delivered a stillborn baby at term in another province. The patient has been adherent to his medication as evidenced by blood drug concentrations. Biochemical and haematological parameters were regularly monitored. Renal function deteriorated transiently at 7 months, but improved on adjustment of the tacrolimus dose. Other laboratory tests remained within normal limits. Specifically, with reference to tacrolimus use, blood sugar concentrations remained normal. Routine ultrasonography of the kidneys and bladder were normal throughout. Superficial skin sensation improved progressively, from being patchy to becoming fully established with normal touch sensation over the whole penis by 7 months. We did a cost analysis

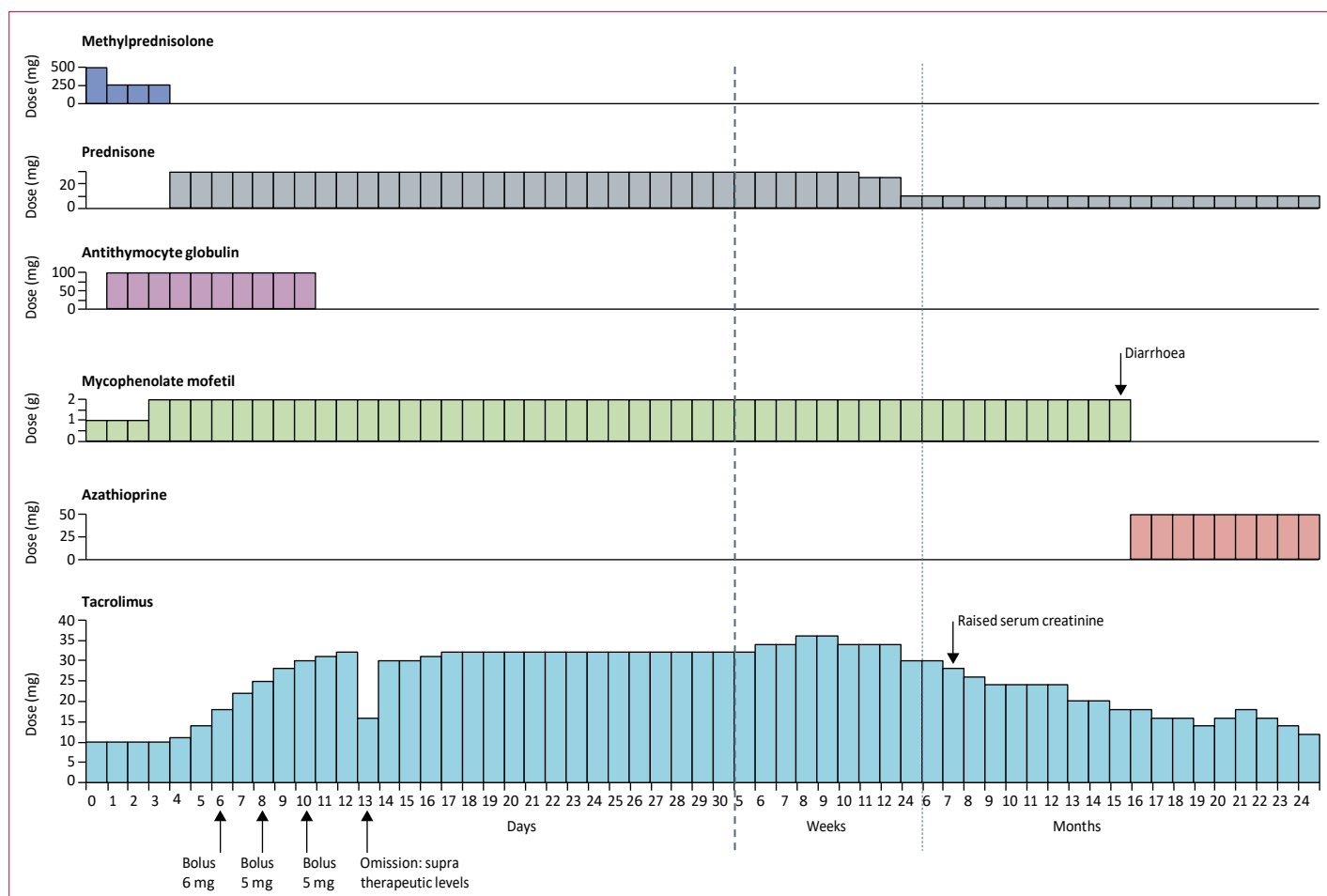


Figure 5: Immunosuppression regimen during follow-up

Day 0 is the day of surgery.

including surgical and anaesthetic services and the first month cost US\$18 653 while immunosuppression and clinic visits in the subsequent 2 months cost \$1184 per month. The cost of treatment continues to be carried by the Western Cape Government.

The slight colour discrepancy, tuft of donor hair, and scarring at the suture line were acceptable to the patient. His SF-36v2 mental health scores improved from 25 before the transplant, to 57 at 6 months and 46 at 24 months post transplant; physical health scores improved from 37 at baseline to 60 at 6 months and 59 at 24 months post surgery. At 24 months the maximum urine flow rate (Q_{max}) was 16.3 mL/s from a volume voided of 109 mL, with a normal flow-time curve. The IIEF showed an overall satisfaction score (domain E) of 8 from a maximum score of 10. The scores for the specific domains were 26 from a maximum of 30 for erectile function (domain A), 8 from a maximum of 10 for orgasmic function (domain B), 9 from a maximum of 10 for sexual desire (domain C), and 12 from a maximum of 15 for intercourse satisfaction (domain D). However, at the 24 month interview, the

recipient admitted that he struggled to have a second erection per night should he wish. He reported that when the second erection did occur, he could have normal intercourse. He declared that this finding remained unchanged from sexual activity soon after the operation. No types of assistance to achieve erections were provided after 3 months post surgery. At a visit 18 months after the transplant, the recipient declared that the most valuable result of his penis transplant was that he is "happy" again; this he ascribed to the complete restoration of all the individual components of penile function and not to any single one of them such as the cosmetic result (figure 6).

Discussion

This study is the first to report a functionally successful penile allotransplant; we deemed the transplant to be successful because the patient is able to urinate normally, achieve erections suitable for vaginal penetration, and experience normal orgasm and ejaculation.

There is an unmet, unquantified need for penile transplantation because of wartime and industrial genital



Figure 6: Cosmetic result at 24 months

injuries, penile malignancies, and severe congenital penile abnormalities.^{3,33} In South Africa, the need for this type of transplant arose because of the relatively large number of post-adolescent young men rendered aphallic following ritual circumcision.⁵

Composite tissue transplantation is complex and technically challenging.^{34,35} Key to the technical success of the surgery is adequacy of the vascular supply to the allograft; although the importance of the arterial supply is obvious, venous drainage is also paramount; establishing sufficient venous drainage for our patient allowed us to reduce the swelling. During the surgery on this patient we mobilised the inferior epigastric artery for anastomosis to the right dorsal artery of the penis as previously described in penile replantation.³⁶ The dorsal arteries of the penis in our patient were obliterated by the previous injury and fibrosis at the time of penile loss. On release of the vascular pedicles, the skin, corpora cavernosa, and corpus spongiosum had visibly good blood supply. We deliberately avoided warming the graft because we were concerned that this might increase the metabolic requirements of the graft and compromise its viability.¹⁵ In our patient the dorsal arteries were clearly supplying the corpora cavernosa and the corpus spongiosum, as shown by cavernosal backflow after release of the vascular clamps. We did not anastomose the very small and contracted cavernosal arteries and this does not seem to have affected the outcome, contrary to a report suggesting that the corpora cavernosa cannot

be supplied by the dorsal arteries of the penis.²⁶ We were concerned about the position of the neo-vasculature that ran across the pubic symphysis (as opposed to emerging from underneath the pubic arch as occurs normally) becoming compressed during sexual intercourse, causing sudden detumescence of the erect penis, but this concern seems to have been unfounded.³⁷ Full sensory recovery occurs in penile replantation and also occurred for our patient; nerves, once approximated grow into nerve sheaths at about the rate of 1 mm per day.³⁸

The penis seems to be a resilient organ and tolerated the cold ischaemia time of 16 h well. A successful penis replantation was described after a patient with psychosis swallowed his self-amputated penis, which was retrieved on gastroscopy 2 h later and reimplanted. He had minimal sensation loss in the otherwise normal functioning penis after surgery.³⁹

The dual psychological impacts on a young man of first losing his penis and then having it replaced, were of concern to us. The self-image, which normally has a fairly solid state, becomes fluid again when adding or removing an organ during transplantation. The loss or gain of an organ can have a devastating effect on the ego; it is described as causing a ripple effect on self-image and might induce psychosis, depression, or even renunciation of the transplanted organ.^{28,40-42} The addition of something as benign as a cardiac pacemaker can induce serious psychological disturbances.⁴³ Our recipient remained emotionally stable throughout the ordeal of the penile loss and the subsequent penile transplant, emphasising the need for careful psychological screening of potential recipients. The patient showed indications of his acceptance and ownership of the graft in his early remark "I want to see my penis", underscoring his eagerness to accept and integrate the penis as part of himself. His comfort with his penis during follow-up suggests that he is unlikely to be suffering from any of the primitive guilt that is sometimes induced by the transplant.²⁸ The recipient's quality of life improved substantially as measured by SF-36v2 scores, which are often used in transplantation and were chosen in this case for ease of interpretation.^{44,45} The decline in the mental component of the score at 24 months compared with 6 months is concerning, especially in the context of the normal IIEF score. This decline might be related to personal stressors at the time of the SF-36v2 survey or because the novelty of having a penis again had declined. The patient works in a stressful environment and lives in an area with high rates of violence and crime, which might be reflected in the survey and could be normal for someone living in this environment. The IIEF scores and Qmax are reassuringly more objective measures of normal penile function.

The patient has tolerated the immunosuppression well, likely because of his good physical health before the transplant. The most serious infective complication he had

was a fungal infection resulting from the immunosuppression. Phaeohyphomycoses, such as *Alternaria* spp, are rare opportunistic fungal infections that predominantly affect the skin in immunocompromised patients, particularly those being treated with mycophenolate mofetil. Systemic dissemination can occur and has a high mortality rate. Treatment regimens however have not been standardised.^{46,47} The preferred treatment is with triazoles, such as itraconazole, which inhibits CYP3A4/5. This substantially enhances the levels of drugs that are metabolised by the liver such as steroids and calcineurin inhibitors.^{48,50} Local antifungal treatment followed by oral terbinafine seems to be safe and has been reported as being successful in a patient who received a heart transplant.⁵⁰ Our patient responded well to topical broad spectrum antifungal treatment alone.

Our findings show that penile allotransplantation is feasible and can result in restoration of sexual function, penile sensation, and normal urination. We also emphasise the importance of careful patient selection in terms of physical health, emotional and psychological stability, and adherence to treatment. Although the results of the transplant have been rewarding, we are aware that the potential long-term consequences of sustained immunosuppression remain a risk and will be monitored for carefully. This case might also be hypothesis generating in that female-to-male gender confirmation surgery might benefit in selected cases, revascularisation in vasculogenic impotence might be revisited, and other causes of complete loss of the pendulous penis might be addressed in this manner in future. We are now recruiting for a trial of penile transplantation, which is registered on ClinicalTrials.gov, number NCT03149692. This case report gives hope to those with severe genital injuries or loss, who must often suffer in silence as they are too embarrassed to speak out.

Contributors

AvdM conceived the research question, did the literature search, got the ethics clearance, led the surgery, and contributed to the protocol, surgical planning, data collection, and drafting of the manuscript. ADZ created the figures used in the manuscript, assisted in surgery, presented the data at an international congress, and contributed to the drafting of the manuscript, and data collection. FG and AZ advised on the protocol, surgical planning, microsurgery, and drafting of the manuscript. NWB was responsible for the ethical planning, the ethics components of the protocol, and the drafting of the manuscript, particularly the sections on ethics. DO, HA, TA-Q, and PVS contributed to the data collection and drafting of the manuscript and assisted with surgery. BB advised on the cultural issues of the Xhosa patients, did the preoperative assessment, and contributed to the data collection, particularly the preoperative data, and editing of the manuscript, particularly the introduction and background sections. KB contributed to the data collection, particularly the immunosuppression data, drafted the graphics, and reviewed manuscript. JDN contributed to the drafting of the protocol and manuscript for immunosuppression. MRM was the study supervisor and contributed to the drafting of the protocol and manuscript. JTV helped with the SF 36 research during the planning of the study and obtained the software and contributed to the preoperative data collection and drafting of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

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Update on the status of the first penile transplant recipient at six years and six months

The recipient is currently 27 years old (as of 2020). He is well, having spontaneous erections without medical assistance that are sufficient for intercourse, he stands to urinate, and he has made a full psychological recovery. His renal function is normal, and he is generally compliant with immunosuppressive medication, but not completely. He works as a security guard. His penis appeared normal and functioned well (Figure 1). Since the first report (Van der Merwe et al. 2014), he has become more promiscuous and reported having sexual intercourse up to seven times per day and has several sexual partners. His relationship with his long-time partner floundered several months after she delivered a full-term but stillborn baby in 2015. He continued his hobby of bodybuilding and fared well in competitions.

During September of 2017, his penis started undergoing skin changes. This was despite normal to slightly reduced erectile function (he could not have as frequent intercourse as before). Biopsies were non-specific, although repeated biopsy demonstrated features of chronic rejection. The rejection occurred suddenly. Attempts



Figure 1: The transplanted penis in August 2016.

were made to reverse the rejection medically but with no satisfactory results. Serum tacrolimus levels were erratic and it soon became clear why. His partner at the time informed us that he had stopped medication before the body building competitions and then resumed the medication after the competitions. He stopped the medication to avoid the immunosuppressive medication-related skin side effect of a fine macullopapillary rash over his shoulders and trunk.

Histology, at first non-specific, demonstrated chronic rejection. His penile shaft skin started to mummify (Figure 2A), and necrotic tissue had to be removed between January 2018 and July 2018. Split skin grafts adhered poorly (Figure 2B). Eventually, islands of skin grafts coalesced.



Figure 2: A. Penile shaft skin starting to mummify. B. Loss of the glans penis, a segment of penile shaft and poor split skin graft results despite additional hyperbaric oxygen treatment.

As he resumed immunosuppression medication compliance, his erectile function improved, although he lost a significant portion of his penis. His promiscuous behaviour returned. He contracted a sexually transmitted disease (STI) in August 2019 (Figure 4A) and again in June 2020.

He was treated for sexually transmitted disease on both occasions with ceftriaxone 250 mg intramuscular, azithromycin 1 g orally, and metronidazole 2 g orally. He made a rapid recovery after each treatment but developed meatal stenosis in July 2020 (Figure 4B).

The meatal stenosis was operated with a meatotomy operation in which the urethral mucosa was sutured to the skin (Figure 5).



Figure 4: A. Sexually transmitted disease in the transplanted penis. B. Meatal stenosis followed.



Figure 5: Post-operative the meatotomy operation. Photographs were taken in July 2020.

He reported that the meatotomy improved his urination as well as his ejaculation. He expressed great regret at his non-adherent behaviour which had compromised his graft. He remains human immunodeficiency virus (HIV) negative.

Considering a potential shift in the risk-benefit ratio of the immunosuppression medication and penile remnant, he was counseled to reconsider phalloplasty. He strongly declined.

CHAPTER 2

Lessons learned from the world's first successful penis allotransplantation

This chapter consists of a published manuscript in which we discuss the lessons learned from the first successful penile transplantation. While there was a great need for penile transplant guidelines, and while some constructed guidelines without transplanting a penis [1], we felt it was too early to suggest guidelines. However, building on the foundations of the lessons learned in our own context, we offered preliminary insights to guide others in adapting the procedure to their unique environments. The development of comprehensive and evidence-based guidelines are underway.


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Lessons learned from the world's first successful penis allotransplantation

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Abstract We performed a successful penis allotransplantation on 11 December 2014. Sharing the lessons learned might help more patients in need to be treated this way. We divided the project into manageable segments that was each overseen by an expert. The ethical review and conduct paved the way for a publically acceptable and successful project. Screening for a psychological stable recipient is important. The most difficult part of the project was finding a donor penis. This was successfully negotiated with the family of a brain dead donor by creating a neophallus for the donor, thereby maintaining the dignity of the donor. Working with transplant coordinators that are sympathetic to aphallic men is crucial. Surgeons versed in microvascular techniques is a critical part of the team. Transplant immunologists have to adapt to treat composite tissue transplantation patients.

Graphical Abstract



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1 Introduction

Vascularized composite tissue allotransplantation (VCA) is an established frontier in reconstructive surgery [1]. Our team performed a successful penis transplantation on 11 December 2014, after a period of planning and research. A similar procedure had previously been attempted at an institution in China, but failed due to the patient's partner insisting removal of the graft that had superficial skin necrosis early post-operatively [2].

This was a challenging project to complete successfully. We share the lessons that were learned so as to hopefully enable other centres to follow suit and ultimately contribute to helping a distressed and vulnerable patient population in need of penis transplantation.

1.1 Lesson 1. Correct indication

The only appropriate indications for penis transplantation are loss of the entire pendulous penis or absence of a penis in a patient that should have one, as is in major congenital malformations. Offering this procedure to males who perceive their genitalia as too small would be inappropriate; the risks associated with the procedure itself and also a lifetime of immune suppression treatment may lead to serious complications and eventually even leave the recipient aphallic. Furthermore, with the dire donor penis shortage organs should be used to assist those patients in real need. (Figs. 1 and 2)

1.2 Lesson 2. Divide the project up into segments and have an expert oversee each segment

From the start, we divided the project into separate segments, commencing right at the stage of Ethics Review Board submission. Expert consultants from the following disciplines were co-opted in order to maximise the chance of success:

- Forensic pathologist—To advise on the legal issues surrounding the transplantation of a penis from a deceased donor.
- Ethicist—with a mandate to make sure all proceedings adhere to good ethical practice.
- Transplant coordinator
- Psychologist—For ongoing input in both the pre- and post-operative periods
- Transplantation nephrologists—To Manage the immunosuppressive regimens. Our renal team adapted well to the novelty of caring for the participant.
- Plastic surgeons versed in microvascular surgery.
- Media liaison officer—Provided by our academic institution (University of Stellenbosch)
- Pathologist and dermatologist—Tasked with acquainting themselves with the unique aspects of VCA rejection.
- Team of nurses trained in the care of immunosuppressed transplant patients

1.3 Lesson 3. Ethical issues are a minefield

We benefitted much by having a dedicated applied ethicist on the team. Careful consideration during the planning



Fig. 1 Penile allograft at the end of surgery. Note the urinary catheter that should have been placed suprapubically

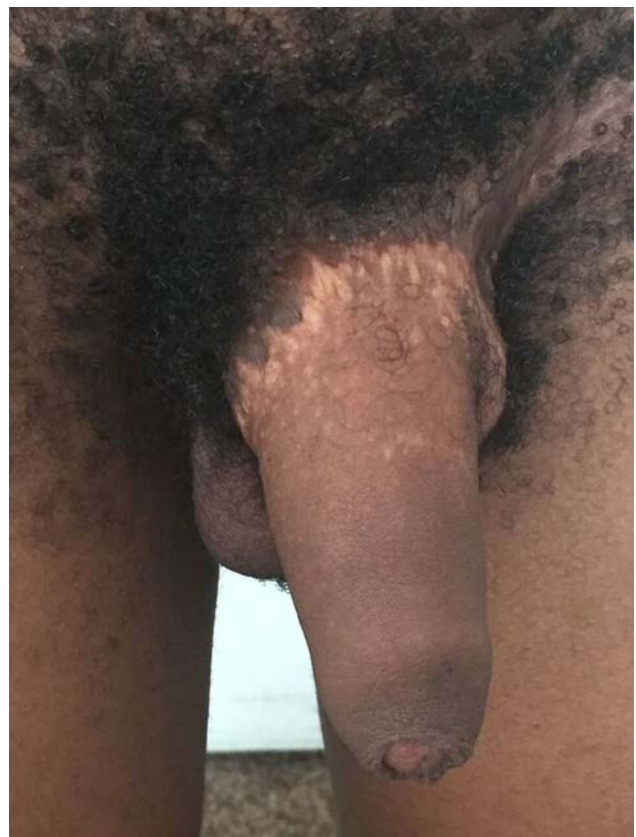


Fig. 2 The penile allograft at 20 months post-operatively

phase of our study allowed us to anticipate potential pitfalls, two of which are worth mentioning here:

- 1) *Minimise therapeutic misconception:* Therapeutic misconception indicates a participant's failure to appreciate the difference between research and treatment. This can include an overestimation of clinical benefit from an experimental intervention, as well as underestimation of potential risk of harm [3, 4]. We implemented a rigorous informed consent process. Our participant was counselled over a 2-year period, prior to transplantation, and this allowed us the opportunity to promote and assess our participants' understanding of the risks involved and to promote truly informed and voluntary consent to the experimental procedure.
- 2) *Appropriately mitigate risk:* Our ethicist's inputs heightened awareness of, and spelled out risk mitigation steps for the emotional, social and psychological risks that our research participants might experience, in addition to the physical risks (including the myriad of potential side effects of long term immunosuppression). Based on these inputs our first transplant participant was selected to minimize risk. A number of participants were eligible for scientific reasons, but at substantially higher risk of physical and psychological harm. This particular patient was considered physically and psychologically suitable for VCA and was selected as the first research participant based on his favourable lower-risk profile.

1.4 Lesson 4. Psychological issues must be addressed in the recipient

The screening process used for our possible penis transplant recipients was similar to that used in our renal transplant program. However, we were very cognisant of the potential additional risk associated with receiving someone else's penis as far as conflicting the ego and disturbing of the self-image are concerned. A subsequent "ripple-effect" on the ego has previously been described and is associated with the very real risk of inducing psychosis. Although this may also occur as a consequence of renal (or any other organ) transplantation, the risk is higher in the case of a urogenital organ such as the penis [5–7]. In addition, the high-dose of steroids that was given as induction of immunosuppression, is known to be a separate risk factor for the development of acute psychosis [8].

1.5 Lesson 5. Practice on a cadaver

Despite the fact that we had been fully trained as urologists and are clinically active as part of a tertiary care urology

service, we benefitted significantly from a focused dissection on a cadaver model. Harvesting of the dorsal neurovascular bundle below the symphysis pubis demonstrated the difference in vessel diameter between the proximal and the distal parts of the penis. We also realized that harvesting the penis so proximally allowed for approximately 3 cm of corpora cavernosa, as well as approximately 2 cm of urethra and corpus spongiosum to be removed, leaving an elongated vascular pedicle that would offer very valuable mobility during anastomoses.

1.6 Lesson 6. Reconstruct a phallus for the brain dead donor

The crucial turning point in our project we think was when we offered the families of the potential penis donor the option of having a phallus created from the lower abdominal skin, following removal of their deceased relative's penis. It was clear that this gesture brought a definite change to the relatives' perception of penis donation: where families would previously reflexively refuse donation of their deceased relative's penis, they were now actually thinking before saying "no" with one family eventually agreeing. Our interpretation of this phenomena is that it is seen as restoring the dignity of the brain-dead donor in the eyes of the family. It appears that no family would agree to their relative entering the grave without his penis, or at least the semblance of a penis.

1.7 Lesson 7. Cool the harvested penis by direct intracorporeal injection of a standard transplant solution

The dissection of the dorsal neurovasculature and transection of the corpora induced spasm of the dorsal and cavernosal arteries, which resulted in our being unable to cannulate the vessels for the purpose of infusing the cooled organ preservation solution (Custodial™). We therefore proceeded to inject the Custodial™ solution directly into the corpora cavernosa from the left side of the penis. Clear fluid could be seen flowing from the severed ends of the spongiosum, cavernosal bodies and dorsal veins of the penis. If clear fluid fails to extrude from the spongiosum then an additional injection of cooled Custodial™ could be performed directly into the glans penis—this should irrigate the entire corpus spongiosum and may even overcome possible vascular drainage differences in the donor penis [9, 10].

1.8 Lesson 8. Surgical principles that help

Consider using the deep inferior epigastric blood vessels to supply blood to the graft penis early on in the surgery, ignoring the native dorsal penile vessels. We wasted several

hours trying to dissect out the recipient's dorsal neurovascular complex, only to ultimately find the structures to have been obliterated as a complication of the previous infective process that was the original cause of penile loss. Utilising the deep inferior epigastric vessels supplied suitable diameter blood vessels with good flow and with a lot less effort.

The donor penis must be harvested underneath the pubic symphysis taking care to preserve the dorsal neurovasculature at its largest diameter. The donor penis, after having been cooled to 4 degrees Celsius, can then be prepared for transplantation on the bench by dissecting the dorsal neurovascular bundle free for a distance of about four centimetres. The proximal corpora and urethra are then trimmed but a slightly extended urethra is left to enable wide spatulation and tension-free anastomosis with the native urethra. We used interrupted sutures for the urethral anastomosis but in future will use a bi-layer of continuous mucosal sutures as well as a continuous suture to the outer corpus spongiosum as this will facilitate drainage via the corpus spongiosum itself.

It is absolutely imperative to have surgeons on the team who are experienced in performing microvascular anastomoses.

As was evident in our case, it is not essential to perform anastomosis of the cavernosal arteries, provided that good perfusion of the corpora cavernosa is attained by dorsal penile arterial supply. Intra-operatively we visualized copious amounts of bright red blood flowing freely from the severed spongiosal- and cavernosal ends after completion of the dorsal penile arterial anastomoses. This indicated adequate cavernosal blood flow despite having no anastomoses of the cavernosal arteries. The recipient's normal erectile function which started around 3 weeks post-operatively, further attests to this.

1.8.1 Use state-of-the art equipment

The dissection of the donor and recipient vessels and nerves require specialized microsurgical equipment that allow handling of structures with 1 mm diameter. This includes instruments, clamps, cannulas (to flush the lumen of the vessels), sutures and optical equipment (loupes, microscope). To improve speed and patency of the venous anastomosis we recommend the use of a GEM Microvascular Anastomotic COUPLER™ ring (Synovis Micro Companies Alliance Inc., Birmingham, Alabama). Besides clinical monitoring we propose the use of a Licox® monitor (Integra LifeSciences, Plainsboro, NJ), which measures the graft oxygen partial pressure and allows early detection of a vascular thrombus. Thrombectomy and reanastomosis can then be performed immediately to salvage the transplant as occurred in our participant.

1.8.2 Be prepared for anatomical variants

A superficial dorsal vein was not present in the donor penis and the recipient dorsal penis vessels were not patent. Plan alternative blood supply options before the operation and be flexible during the procedure to optimise arterial supply and venous outflow.

1.9 Lesson 9. Avoid using a trans-urethral catheter post-operatively—rather use a suprapubic catheter for bladder drainage

We encountered a problematic post-operative wound haematoma and infection, which was likely complicated by the presence of a urinary catheter in the urethra.

1.10 Lesson 10. Immunosuppression by the most experienced transplant immunologists available

Composite tissue transplantation is still in its infancy compared to solid organ transplantation and much remains to be learned about the optimum use of immunosuppression in this form of transplantation [11–13]. Our immunosuppression regimen was premised on the skin being the most immunogenic component of the composite, although there is evidence that the risk of acute rejection of the skin is mitigated when it forms part of composite tissue transplant [14]. Nevertheless, we opted to maximise prophylactic immunosuppression, with induction therapy consisting of antithymocyte globulin and high dose steroids followed by maintenance with tacrolimus, mycophenolate mofetil and prednisone. These are some of the agents currently in use in composite tissue transplants [12]. The choice of polyclonal over monoclonal antibodies was purely an economic one, dictated by our unaffordability of the latter. The adequacy of our immunosuppression is attested to by the lack of any acute rejection. The graft was regularly monitored visually for any signs of rejection, especially initially. A future consideration is the implantation of a distal sentinel skin flap that can be biopsied without too much discomfort to the patient and that could be an early alert to acute rejection [15].

Having established that we had evidently avoided acute rejection, the question of whether we had over-immunosuppressed our recipient arose, when the patient developed an unusual fungal infection of his foot. This was a rare phaeohyphomycosis infection by the ubiquitous saprophyte *Alternaria alternata* and occurred 8 months after the transplant. The infection responded well, albeit slowly, to treatment. Controversy still prevails regarding the most appropriate treatment for this opportunistic infection, although a combination of topical treatment, surgery and systemic antifungal treatment may be required; in a recent

review systemic itraconazole was the most commonly used antifungal agent [16]. The disease is generally localised and seldom systemic. To date only a single possible mortality related to this infection has been reported [16, 17]. In view of this and the risks of using the various ‘conazoles’ (especially drug-drug interactions) and amphotericin B (especially its nephrotoxicity) we opted to treat the patient with surgery and a broad spectrum topical antifungal agent. The risks alternariosis are higher in solid organ transplants other than kidney transplants that are immunosuppressed more intensely [17]. To reduce the risk of infections, we would consider deescalating immunosuppression earlier in future rather than the delayed protocol we had followed in this patient.

Another important consequence of our immunosuppression was the transient decline in renal function blood levels. Tacrolimus dose was adjusted to maintain serum trough levels 10–15 ng/ml. After 10 months a marked elevation of the serum creatinine was noted and in the absence of any risk factors for declining renal function, the dose of tacrolimus was reduced and levels were maintained at 5–10 ng/ml. With this adjustment in tacrolimus dose, the renal function improved, but the long-term impact on kidney function of the tacrolimus is of concern in this young man [18, 19] as end stage kidney failure can occur in up to 28% of recipient of non-renal transplants [20]. The options we have are to reduce the risk of kidney injury is minimising calcineurin inhibitors—in our kidney transplant patients we reduce the dose of calcineurin inhibitors at 3 months, although this approach is refuted by the finding by Nankivell et al. [18] that the correlation calcineurin inhibitors dose and the renal pathological injury is poor. The alternative is to switch to calcineurin inhibitors sparing regimen that includes and mammalian target of rapamicin inhibitors, but these are associated with an increased of acute rejection [21].

1.11 Lesson 11. Obtain buy-in from hospital management

In the prevailing economic environment in South Africa it was very challenging to obtain adequate funding for all aspects of this project, and the majority of the cost would have to be regarded as forming part of a clinical incident. This represents a significant additional financial burden on our already constrained hospital budget, which could have caused hospital management to refuse to allow for this (essentially experimental procedure) to be performed in their hospital. We had frank and open discussion with the hospital management in 2011 that eventually led to their agreement to bear the cost of this project, when other sources of funding could not be obtained.

1.12 Lesson 12. Work with transplant coordinators who are sympathetic to a phallic men

We found that not all transplant coordinators were sympathetic towards the project or the potential recipients—for unknown and possibly deeply-rooted personal reasons. We speculate that this may be due to the coordinators’ perception of the need for normal sexuality or the fear that asking for a donor penis may jeopardise the interview with a deceased’s family when asking for the donation of other solid organs. Working with coordinators who do not approve of the project and have not fully bought into it, is sure to make finding penile donors extremely difficult. Fortunately, our team had a transplant coordinator who proved to be passionate about helping the recipients and she was the only person who engaged all of the potential donors’ families to discuss possible donation.

1.13 Lesson 13. Handling the media

We were surprised and overwhelmed by the media attention that this operation created because we considered the hype to be out of proportion to the complexity of the surgery or the project. It does, however, underscore the public interest in transplantation—in particular when genitalia are involved. From attempts at facial transplantation in the United Kingdom we learned that the media could easily cause a public outcry in response to such a dramatic procedure, which may bring the project to a halt [22–24]. We avoided publicising details of the operation to assure ourselves of the success of the procedure and to deal calmly with the clinical issues. The 3-month delay meant we could announce the success of the procedure with a fair amount of certainty. Having one media spokesperson for the team (team leader) and a media liaison officer are essential. All interviews should be monitored so that conflicting reports do not cause public confusion. It is important that the media officer screen all requests for interviews in order to avoid media houses taking a light-hearted or sexually perverse angle on the procedure.

2 Conclusion

Of all the factors listed above the most challenging for us was finding a donor penis. Potential donor families should be engaged respectfully by a motivated transplant coordinator. Protecting the dignity of the brain-dead donor by offering a skin phallus should be communicated and prioritized very early. Reconstructing a skin phallus for the donor that protected the donor’s dignity was the crucial turning point in our project.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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CHAPTER 3

Penis allotransplantation for penis amputation following ritual circumcision: Report of a second case with 40 months follow-up

This chapter consists of a publication-ready manuscript in which we discuss our second case of penile transplantation. At the time, this was the third successful penile transplant globally.

Penis allotransplantation for penis amputation following ritual circumcision. Report of a second case with 40 months follow-up

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Penis allotransplantation for penis amputation following ritual circumcision. Report of a second case with 40 months follow-up

Summary

Introduction

Ritual circumcision, a leading cause of penile amputations worldwide, is a rite of passage that remains important within certain South African cultures. Due to the donor site morbidity of phalloplasties, the outcomes, and complications of traditional reconstructive surgery, alternative treatments were sought. Following our first successful penile transplant operation in 2014, we now report on our second successful transplant performed in 2017.

Methods

Having gained valuable experience from our first case, as well as the success of the reported American cases, we recruited a second patient for penile allotransplantation. The recipient was screened in 2013 for psychological and physical suitability. A suitable immunologically matched deceased donor became available in April 2017, and penile and renal retrieval were performed concurrently. After cooling the penis to 4°C, it was prepared on the bench. The organ was implanted using both deep inferior epigastric arteries and one cavernosal artery as the arterial blood supply. Venous drainage was via a single dorsal vein of the penis anastomosed with the left saphenous vein. Dorsal nerves of the penis were anastomosed. Immunosuppression was induced with antithymocyte globulin, methylprednisolone, and maintained with tacrolimus, mycophenolate mofetil, and prednisone. Tadalafil was administered daily for three months. The patient follow-up included self-reported outcomes in terms of erections, return to sexual activity, and urinating standing. Improvement in general wellbeing was evaluated with in-depth interviews using qualitative research methods. Adherence to immunosuppressive regime and complications while on immunosuppression were also documented.

Findings

The first warm ischemia time was six minutes, and the cold ischemia time five hours. The time from ice until reperfusion was six hours thirty minutes (second warm ischemia time). The surgery lasted nine hours, fifteen minutes. Minor skin necrosis needed

debridement on postoperative day 13. The patient reported full but painful erections a month post-surgery. Normal erections persisted after tadalafil was discontinued at three months. The recipient suffered acute kidney injury four months postoperatively, due to a combination of toxic tacrolimus levels and the use of non-steroidal anti-inflammatory medication for a presumed viral infection. His renal function did improve but remained impaired. He was diagnosed with Banff 3 chronic rejection of his allograft at 32 months. He delayed sexual intercourse until eight months postoperatively and reported this to be 'normal again.' His erectile function deteriorated in the eight months preceding the diagnosis of chronic rejection. Currently, he stands to urinate without any lower urinary tract symptoms and has made a full psychological recovery.

Introduction

Penile loss and deaths from the rite of passage of ritual circumcision persist despite efforts by the South African Government to reduce these complications. Many circumcisionists allowed to perform these rituals are still unskilled, inexperienced, and abusive. [1;2] Ritual circumcision related deaths are a common cause of death in young men in South Africa; the custom is also shrouded in secrecy. [3-6] Due to the secrecy, conventional methods of penile reconstruction using a vascularized radial forearm fascio-cutaneous free flap (RFFF) are not desirable. The donor graft site is visible, giving a clue to failed ritual circumcision and may impede manual labour. The results of phalloplasty are less than perfect even in expert hands with the added capital expense of penile implantation. Rates of urethral strictures or fistulae, flap shrinkage, and prosthesis extrusion with multiple procedures are significant. [7-10] Three previous successful penile transplants have been performed: one in South Africa in 2014 [11] and two in the USA in 2016 and 2018 [12;13]. We report our second penile transplantation in terms of self-reported return of urinary function, sexual function, and general wellbeing on a strict immunosuppressive medication regime.

Methods

Setting

Our Renal Transplant Unit, operational since 1976, also cares for our penile transplantation patients. It is situated in a tertiary academic hospital. The nephrologists are responsible for all immunosuppression. They are supported by a team of urologists and a trauma surgeon. The penile transplant programme also has a team ethicist. For the penile transplant, the assistance of a plastic surgeon was sought.

Preparation and patient selection

We performed a cadaver penile transplantation in the run-up to the first penis transplant to familiarise ourselves with the anatomy of the procedure. Our first penis transplant has been reported.[11] Immunosuppressive therapy regimes were established during our previous case, as well as learnings from other penile and facial transplants. [14-16] Ethical principles were based on Emmanuel's eight criteria and 32 qualifying benchmarks, which are, amongst others, informed consent, risk-benefit ratio, and non-maleficence. [17]

We recruited males 18 years or older who suffered a complete penile loss after ritual circumcision and who were unable to have penetrative sexual intercourse, nor were they able to urinate standing. Human immunodeficiency virus (HIV), tuberculosis, and hepatitis B positive patients were excluded. Mental instability and substance abuse were exclusion criteria. Psychological, physical, and laboratory screening tests related to organ transplantation were completed as previously reported. [11] No imaging studies were done as the anatomy after penile loss from ritual circumcision is relatively undisturbed. The transplant recipient was selected from a waiting list of 14 cases based on matching blood groups, negative antibody cross-match, and favourable HLA-antigen matching. We report the outcomes based on the patient's report of his sexual and urinary function as well as his general wellbeing.

The recipient

The recipient lost his penis after a ritual circumcision in 1999. He was recruited to the program in 2013 after a failed penile lengthening procedure in 2012. The penis remnant did not allow him to urinate standing nor have penetrative sexual intercourse. While on the waiting list, he was admitted twice with suicide ideation coupled with ethanol abuse. The psychiatric evaluation concluded that ethanol abuse was a coping mechanism due to the traumatic events, and the penile transplantation should be 'curative.' He was healthy, except for the discovery of blood pressure elevation the day prior surgery. He was of blood group A. Panel reactive antibody tests (PRA) performed at the time of listing showed only 6% Class 1 antibodies positive; the last PRA tests prior to transplantation, in 2016, demonstrated 0% Class 1 antibodies but 20% Class 2 antibodies. At the time of surgery, he was 38-years old and had been waitlisted for four years.

The donor

A 26-year-old deceased donor with similar blood group A became available in April 2017. The T-cell cross-match between donor and recipient was negative. An abdominal skin phallus to retain dignity and prevent emasculation was offered to the grieving donor family but was declined. The kidneys and penis were the only organs donated.

As the donor's cardiovascular system became unstable, he was rushed to the operating theatre. Penile neurovascular retrieval was, therefore, not as proximal as we would have preferred due to the limited time available for dissection. After a warm ischaemic time of six minutes, the penis was cooled to 4°C, and the dorsal arteries of the penis and corpora cavernosa were flushed with Custodial™ solution [Custodial-histidine-tryptophan-ketoglutarate (Custodial-HTK), Brettschneider; Koehler Chemie, Alsbach-Haenlien, Germany].

The penis was set on a bench to prepare the urethra, corpora cavernosa, corporeal arteries, and dorsal neurovascular structures. Two dorsal arteries of the penis were identified. However, only one deep dorsal vein of the penis was present with the absence of a superficial venous drainage system. Due to the relative distal retrieval of the neurovascular bundle, the arterial diameter was estimated at about 1.5 mm.

For technical reasons, the transplant could not be performed immediately, and the prepared penis was stored in Custodial™ solution for five hours (cold ischemia time). The second warm ischemia time was six hours and thirty minutes.

The transplantation

As there was a significant skin colour discrepancy between the donated penis and the recipient, care was taken to re-consent the recipient for penile transplantation. The options of medical tattooing or a skin graft at a later stage were offered to the patient. After the administration of induction immunosuppressive agents as described previously [11], the recipient received general anesthesia with intra-arterial monitoring. A supra-pubic catheter was placed prior to surgery. [18] The penile remnant was surgically exposed, removing scar tissue covering the penile stump. The corpora cavernosa was freed from the corpus spongiosum to allow for a spatulated urethral anastomosis later.

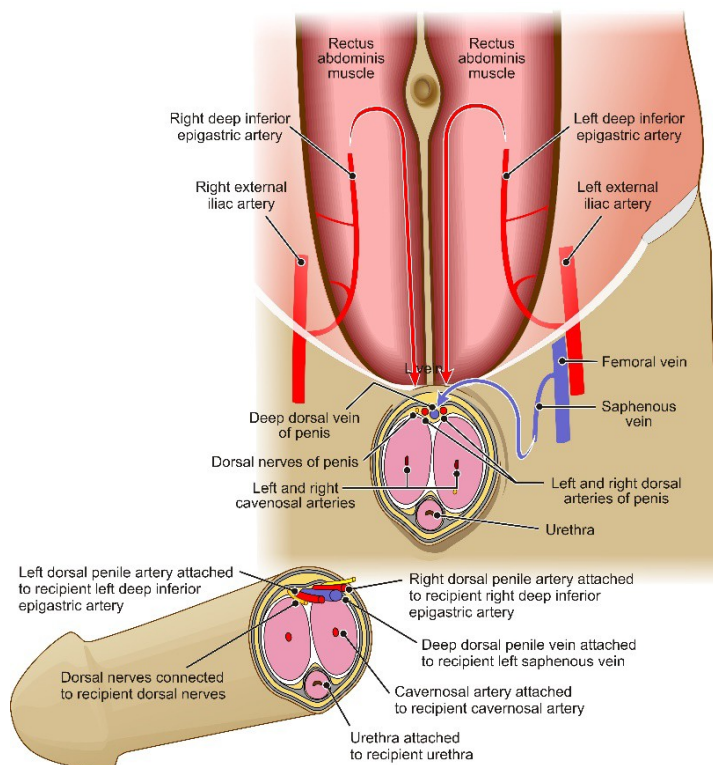


Figure 1. Schematic drawing of the neurovascular anatomy of the transplantation. Note that no superficial dorsal vein complex of the penis was present.

The dorsal nerves of the penis were dissected free from the obliterated and sclerosed dorsal vessels of the penis, ready for anastomosis to the corresponding nerves on the graft. The left and right deep inferior epigastric arteries were exposed via bilateral lower abdominal para-median incisions (Figure 1).

Due to the relatively short dorsal vessels of the donor penis, the deep inferior epigastric vessels had to be dissected distally to a small diameter to correspond to the width of the dorsal arteries of the penis, consuming much operating time. The liberated vessels were transposed under the suprapubic skin bridge to be visible in the operating field superior to the penile stump. Using an operative microscope at six to nine times magnification, we anastomosed the deep inferior epigastric arteries to the dorsal arteries of the penis with interrupted 9/0 nylon sutures. The single deep dorsal vein of the penis was anastomosed to the left saphenous vein using a venous coupling device. The urethras were spatulated, and in contrast to the previous case, the mucosa of the urethra and adventitia of the spongiosum were anastomosed separately to allow venous drainage inside the corpus spongiosum. Urine drainage was via both a suprapubic catheter and transurethral catheter. The transurethral catheter was removed after two days.

The right cavernosal arteries were anastomosed on the right but deemed too small to attempt on the left side. The corpora cavernosa was anastomosed in watertight fashion with 2/0 polyglycolic acid absorbable sutures. Lastly, the dorsal nerves of the penis were anastomosed using 9/0 interrupted nylon sutures. The skin was closed using interrupted 4/0 polyglycolic acid sutures. A corrugated drain was placed in proximity to but not in contact with the vascular anastomoses. During surgery, blood pressure was maintained at a mean arterial pressure of around 75 - 100 mmHg to ensure good graft perfusion. Intra-tissue oxygen tension was monitored with a Licox monitoring system (Intergra Neurosciences, Plainsboro, N.J. USA). Postoperatively, a cradle was placed over the genital area to prevent pressure from bedding on the fine anastomotic lines.

Immunosuppression induction was similar to our previous reported case with antithymocyte globulin (ATG) for ten days, methylprednisolone, tacrolimus, mycophenolate mofetil, and prednisone. The patient was kept isolated and bedrest while on ATG. Tacrolimus blood levels were monitored daily while in hospital, as were renal function tests.

Postoperative course

Daily visits were restricted to specific team members and the psychologist to minimise the infection risk while the patient was receiving ATG. Aspirin 150mg and heparin 5000 IU subcutaneously twice daily were administered for the first month to prevent arterial thrombosis (experienced with our first case). Dressings were changed daily, and chloramphenicol ointment applied to keep the penis skin soft and supple. Tumescence of the graft was visible at morning dressing changes, and the patient reported painful nocturnal erections at a week.

The graft remained pink and well perfused; however, previously dusky areas at the base of the penis became small necrotic areas of skin on the suture line. Necrotic skin islands were debrided on day 13 (Figure 2A). Due to the amount of skin left on the graft, the defect could easily be closed. Tissue cultures were negative for bacteria and fungi. The swelling of the graft persisted for weeks. (Figure 2B).



Figure 2. A. Small areas of necrotic skin at the base of the penis needed debridement. B. After successful debridement of necrotic skin, swelling remained for several weeks.

On day 18, urine was passed inadvertently via the graft due to an overfull collection bag. On day 22, he reported full erections. On day 25, the attending psychologist said he was 'impressed' with the patient's attitude. He was discharged on day 33. On day 39, he was re-admitted for a urethrogram that demonstrated a small sinus at the suture line; the suprapubic catheter, therefore, was retained.

Repeat urethrogram at six weeks excluded urinary leaks, and the suprapubic catheter was removed. On day 83, he was noted to have a serum tacrolimus level of 20.2 ng/ml. His renal function had deteriorated with a serum creatinine value of 153 $\mu\text{mol/l}$. On day 100, his renal function had deteriorated even further with a serum creatinine value of 530 $\mu\text{mol/l}$; he was found to have a markedly elevated serum tacrolimus level of 20 ng/l. It transpired that he had also used non-steroidal anti-inflammatory medication for flu-like symptoms during the preceding weeks. Urine microscopy revealed muddy brown granular casts suggesting acute tubular necrosis as the cause of his acute kidney injury (AKI). He was hospitalised, the dose of tacrolimus was reduced, and his non-steroidal anti-inflammatory medication discontinued; he was maintained on intravenous fluid management until renal function had improved. He was discharged with a serum creatinine of 150 $\mu\text{mol/l}$.

He was treated for the first three months with tadalafil 5mg daily. Eight months post-transplant wounds were healed, and sensation fully recovered. At 22 months, the penis was still healthy (Figure 3A), and he engaged in regular penetrative sexual intercourse. No medication was needed to achieve erections sufficient for intercourse. His partner left for another province due to work-related reasons. While he was not sexually active any longer, he reported that his erections remained normal. There was a significant improvement in his wellbeing.

During February 2019, he was admitted for the management of community-acquired pneumonia that caused a transient worsening of his renal failure.

In June 2019, he developed penile pain and itching of the skin with sub-therapeutic serum tacrolimus levels of 4.3 ng/l. A month later, the tacrolimus levels were undetectable, suggesting non-adherence to his medication. We also suspected that he was abusing ethanol again to cope with the loss of his partner to another province and being unemployed. He received intravenous pulse methylprednisolone daily, with doses of 500mg, 250mg, and 250mg over three consecutive days, that resulted in a



Figure 3A. The result at 22 months post-transplant. B. Chronic skin changes and non-healing ulcers of chronic rejection – Banff Grade 3 chronic rejection was diagnosed during March 2020, picture as seen on 20 July 2020, two months after plasma exchange.

reduction of genital pain. A biopsy revealed only non-specific inflammation. His erections reportedly remained normal. He was not sexually active as he had no sexual partner at this time.

From October 2019 to December 2019, he developed two ulcers on the penis and experienced reduced erectile function. Erections improved on tadalafil 5mg, but his penile pain recurred. In January 2020, he continued to report penile pain and non-healing ulcers on the proximal shaft of the penis and weak erections (Figure 3B).

In February 2020, he underwent a graft skin biopsy that was reported a Banff Grade III chronic rejection. In March 2020, he received a repeat of the daily pulse methylprednisolone of 500mg, 250mg, and 250 mg consecutively over three days with a subsequent increase in his oral prednisone dose to 30 mg daily. Although he experienced some improvement in his genital pain, his erections remained poor. Donor specific antibody tests were requested, and six were found to be present in the HLA A, B and DQ domains, respectively, with mean fluorescence intensity (MFI) between 800 and 7000. In April 2020, he received seven sessions of plasma exchange. Following this PolygamS/D™ (Baxter Inc., Los Angeles, CA) was administered at 100mg/kg for three days. This had a dramatic beneficial effect on penile pain and ulceration.

The cost the first month should be similar to the first case of about 253 000 ZAR. The cost of current of maintenance immunosuppression on 25 September 2020 was 2552 ZAR per month.

The patient reported in 2018 and 2019 on several occasions that he is back to 'normal' referring to his general wellbeing, being sexually active and urinate standing. Unfortunately, he also said that he was still being discriminated against in his community as he had failed the rite of passage. The fact that he looked normal, could urinate standing, and have sexual intercourse had helped him to cope with the ongoing rejection from his community (see Chapter 5).

At the time of writing in August 2020, he was admitted with acute pancreatitis, related to excessive alcohol intake used in the light of his erectile dysfunction and being unemployed. He is currently under the care of the hospital psychologist.

Discussion

Our second penile transplant supports the 'proof of concept' that we sought to establish

in our first report. [11] The restoration of normal genital anatomy was accompanied by

physiological recovery, with the ability to urinate standing and restoration of sexual function. The restoration of physiological function was also accompanied by psychological recovery. These physiological and psychological recoveries occurred in a relatively short time. The three most beneficial aspects of penile transplantation - in line with results from the two American penile transplants done in 2016 and 2018. [12;13] The rapid functional and psychological recovery is in contrast to phalloplasty, where difficulties initiating and seeking sexual contact as well as difficulties achieving orgasm are of the main concerns. [19] Also, complications associated with phalloplasty [20] drives the search for a new type of treatment for aphallic men.

The success of the penile transplant was marred by a challenge all too common in transplanted patients. Adherence, in this case, and in our first case, remains an area of concern. Due to social difficulties in our community, we lose 40% of renal transplants due to non-adherence. Recipient age below 40 is a risk factor for non-adherence in our setting for renal transplantation. [21;22] Once a patient is non-adherent, it is difficult or impossible to reverse the anatomical and physiological damage even if adherence to medication is restarted. This case demonstrates that penile skin that rejects may become thickened with ulcerative lesions making intercourse difficult. The erectile function will also decrease with immunological rejection as the corpora cavernosa vascular endothelium is vulnerable to immune modulated damage. [23] In addition to the cost to the patient in terms of his quality of life, the financial costs of attempting to salvage a failing graft are not insubstantial.

The deterioration in his renal function is also a great concern. There is a possibility that he may need renal replacement therapy in the future as he is, according to the Kidney Outcomes Quality Initiative (KDOQI), [24] in Stage 3a renal impairment (mild to moderate renal impairment). While this possibility was discussed with him at obtaining informed consent, the toxic tacrolimus levels, in addition to NSAIDs medication he used against our advice, caused an acute kidney injury that could have been prevented.

The lessons we learn from this case, in the context of our first case of penile transplantation, is that relatively rapid, virtually complete anatomical, functional, and psychological recovery is possible with penile transplantation. This follows the Gillies "Commandments" of reconstructive surgery, stating that replacing "like with like" tissues will have superior results. [25]

The second important lesson is that adherence can undo a good medical result. In our setting, though, we should attempt to select cases more carefully to mitigate the challenge of non-adherence. While we believed that penile transplant would "cure" his alcohol problem, the benefit only lasted temporarily, and he reverted back to ethanol as a coping mechanism when experiencing difficult times, causing non-adherence to medication. While screening for future non-adherence is difficult, we will be stricter in selecting patients, and a more thorough psychological screen would be important, accompanied by even more careful and regular patient education.

Conclusion

The loss of a penis is devastating to the patient; complete self-reported urinary, sexual and psychological recovery is possible with penile transplantation. Concerns about future renal function exist in this case as mild to moderate renal impairment is present. Non-adherence to medication and alcohol abuse is a concern in this case. Due to the young age of potential penile transplant recipients screening to allow recipients on the program should be rigorous. Safe immunosuppression management is needed to propel penile transplantation forward as a viable treatment option for the loss of phallus.

Conflicts of interest

None declared

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CHAPTER 4

Ethical and societal challenges in penis transplantation

This chapter consists of a publication-ready manuscript in which we discuss the current state of penile transplant ethics in the context of our experience. This manuscript has been submitted for publication in the journal *Current Opinion in Organ Transplantation*.

Ethical and societal challenges in penis transplantation

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Ethical and societal challenges in penis transplantation

Abstract

Purpose of the review: To review the current understanding of the ethical and societal challenges of penile transplantation.

Recent findings: Penile transplantation, as with other forms of vascularized composite allotransplantation (VCA), has gained partial but not full acceptance in society. Guidelines to assist in developing future penile transplant programs in an ethical and scientifically acceptable manner have been created. Controversies regarding the financial costs (to patient and society), patient safety, and patient rights in choosing penile transplant remains.

Summary: Penile transplantation has excellent functional and cosmetic results in the short- and medium-term. The penis, like the face in facial transplantation, carries emotional gravity that relates to visible body parts of another person that lives forth in a tangible manner contributing to psychological and ethical challenges for both the individual and society more broadly, healthcare administrators, and healthcare workers. In the context of these challenges, controversies emerge related to issues of judgment about what society can and wants to afford. Effects of toxic immunosuppression in a non-life saving life-enhancing procedure, as well as costs, become arguments that have to be considered in the context of ethical and societal challenges.

Keywords: Penile transplantation, aphallia, vascular composite allotransplantation, social death, ethics

Abbreviations: VCA – vascular composite tissue allotransplantation
IRB – Institutional review board
REP – regulatory ethics paradigm

Introduction

Penis transplantation follows the Gillies reconstructive surgery commandment of replacing “like with like.”[1] Therefore, excellent cosmetic and functional results were achieved in the four successful cases performed globally between 2014 and 2017. [2**,3,4**,5] As innovative and technically demanding as the penile transplant surgery, and immunosuppression is, perhaps more challenging is navigating the ethical issues

and the societal response. General society took an unexpectedly high interest in penile transplantation, given the limited number of cases done.

Only five cases of penile transplantation have been undertaken so far, of which four were successful. The first case performed in China was reported in 2006 and took approximately four hours to complete and used the blood supply based on a post-amputation replantation model. The penile graft was removed within two weeks due to “psychological” rejection underlining the need for considerations broader than just the physical aspects when dealing with penile transplantation. Photographic images of the graft demonstrated skin necrosis at two weeks that might have influenced the “psychological rejection.” Histology showed segmental epidermis necrosis with no signs of acute rejection. [6;7] The subsequent four cases were performed in South Africa 2014, [5] USA 2016, [2**] South Africa 2017 [3] and an extended penis, scrotum, and abdominal wall transplant in the USA 2018 [4**]. The surgery in these cases lasted between nine and 16 hours each and used blood supply other than the replantation model. Despite early complications such as transplant rejection, fungal infections, and transient renal failure, all four cases made remarkable recoveries in the short and medium-term on all fronts: sexual, urinary, and psychological. Long term data are not available as yet.

While only a few cases have been completed so far, there are questions around the ethics, feasibility, and necessity of penile transplantation. [8-10] Our team was responsible for two of the last four cases, and over the nine years of our study since review board approval in 2011, we have gained useful insights into the complex interplay of societal and ethical matters surrounding penile transplantation. Here we discuss the current state of penile transplant ethics and the associated societal challenges.

Society, the problem and solution for men who are rendered aphallic

Society demands ‘normalcy’, as demonstrated by the history of Joseph Merrick, the disfigured London Elephant man, whose profound wish was to be ‘normal’; however, he was employed by a circus as a curiosity in the latter half of the 1800s. [11] Had society entirely accepted patients such as him with disfiguring deformities or loss, there would likely be a reduced need for replacing visible organs. Agich argues that a certain “yuk” reaction exists in society; this negatively influenced face transplantation initially

and is very likely at the heart of similar responses to penile transplantation. [12] Society, therefore, becomes the unkind mirror in which patients in need of VCA, such as penile transplants, see themselves. The outcry from the British public was so negative that their face transplant program was discontinued awaiting the outcome of a working party investigation by the governing body. [13] The same sentiments have emerged in response to penile transplantation, where members of the public and academia cast doubt over the ethical validity and necessity of the project. [8;10;14;15] One author, despite a three-month delay in media declarations and a 24-month delay in formal reporting of the first successful penile transplant, labeled surgery around penile transplantation as “surgical triumphalism” casting doubt over the motives for the surgery and trivialising the suffering these handicapped men endure. Concerns that a country’s fiscal deficit may suffer because of penile transplantation were also raised. [9]

Society’s paradigm on penile transplantation (and other forms of VCA) is likely also reflected in institutional and regulatory structures such as Research Ethics Committees (RECs) or Institutional Review Boards (IRBs) representing the scientific and lay community. A “Regulatory Ethics Paradigm” (REP) is inherently part of an IRB. [16] The REP of the persons representing the IRB and public may, therefore, fetter innovation such as penile transplantation. The responsibility, for now, to advocate for these silently suffering men thus appears to revert mainly to the treating physicians.

We anticipate that very few members of society would oppose the offer of penile transplantation as treatment option had they been in contact with, or responsible for the treatment of aphallic patients that would qualify for penile transplantation. Any opposition to the idea of penile transplantation is likely based on misinformation about the degree of suffering that these men endure. A barrier for society to learn about their suffering is that patients rendered aphallic socially withdraw, and depending on local cultures and customs are often ostracized. [17-20] Extreme levels of social retraction and isolation cause ‘social death’. Social death, diagnosed by several parameters, including ostracism, was diagnosed in patients awaiting face, hand, and larynx transplants. [21**] Similarly, social death is likely in those awaiting penile transplants due to the known social isolation, retraction, and ostracism. [18-20;22] Ostracism has such severe psychological consequences that it is also titled the “kiss of social death.” [23] In the South African isiXhosa culture, men who fail ritual circumcision are seen as

“dogs” [24] and severely discriminated against. [22;25;26] While American war veterans or penile cancer sufferers needing penile transplant after genital injury or loss likely have less social discrimination than the South African cohort who “failed” the rite of passage to manhood, they likely have comparable experience as post-traumatic stress disorder, and depression are common amongst them as well. [20;27;28]

Society is likely to remain hesitant to accept fully penile transplantation as a form of treatment for genital loss as long as society remains uninformed. In contrast to penile transplantation, for example, the often discriminated against transgender community [29-31] have active advocacy groups in place. [32;33] Society responded in many countries by legally protecting the rights of the transgender community. [34] In contrast, as patients with genital loss appear to withdraw from society with no one to advocate for them, society is likely to remain uninformed. The trivializing of their suffering will, therefore, persist.

Society may be informed via a more focused methodology. Qualitative study methodology explores the depth of experiences of patients that cannot be captured by general interviews or quality of life questionnaires. There is still a dearth of qualitative studies documenting the experiences of all types of VCA recipients/potential recipients, including penile transplantation that could inform society. Lucas, Herrington, and Bramsteadt already used qualitative studies as a tool to document the suffering in genital injury and VCA patients. [20;21**;35**] Bramsteadt concludes that VCA is *life-saving* and not only life-enhancing. [21**] These reports are likely to catalyse more qualitative studies in VCA, including penile transplantation.

Ethical principles guiding penile transplantation

Important lessons for ethical penile transplantation were learned from face transplants. [12;36;37] Perhaps the most important lesson is that ethics is the foundation of the whole project. [6;7;13] Ngaage et al. adopted Beauchamp and Childress’ four bioethical principles (autonomy, beneficence, nonmaleficence, and justice) shaping penile transplantation in comprehensive guidelines aimed at the developed world. [38**] While these cornerstones are well intended, interpretation of ethical principles can be varied and has been labeled “ethics wars” in particular where research is done across country borders. [39] Penile transplant recipients worldwide represent a particularly vulnerable group as they desperately seek ‘normalcy’; penile

transplantation does offer normalcy but at significant sacrifice and cost. Therefore, patients may easily be influenced into accepting risks without due consideration, forming an ethically unacceptable innovative alliance with the research team. A significant power differential exists between the potential recipient and researcher. The South African team, for increased ethical safety, applied in their protocol (available at www.clinicaltrials.gov trial number NCT03149692) the extended principles of ethics research for developing countries developed by Emanuel et al. These eight principles give guidance, and the 31 benchmarks set out to determine to which extent the research satisfies the eight principles. The authors concluded that these principles and benchmarks are useful to guide research in developed as well as developing countries. [40] An adaptation of these principles, Table 1, overlaps and complements the adaptation of Beauchamp and Childress' four bioethical principles modified for penile transplantation by Ngaage. [38**] In the context of the vulnerability of the recipients worldwide, it is prudent to incorporate these principles and applicable benchmarks in penile transplant ethics. [5]

Unpacking and selectively examining the key risks and ethical challenges in penile transplantation

Penile transplantation as a whole may appear ethically more daunting than examining the different aspects of the treatment. Considering the different aspects of the project reveals different levels and types of risk. The risk inherent in the surgery, while often cited as a critically important factor, can likely be well managed and offset by high-quality training in microsurgery and sound relevant knowledge of anatomy of modern surgeons. [46;55*;56] Lessons from animal studies demonstrating that a blood supply other than the usual blood supply of the penis should be used. [57-59] Similarly, one animal study used penile "own" blood supply similar to simple replantation and had up to 40% penile glans necrosis rates.[60] Penile transplant surgery is therefore in the broad sense a vascularized pedicle free flap and as long as this is performed by a team of plastic surgeons, urologists and transplant surgeons complementing each other's skills and knowledge the risks should be acceptable if done according to the IDEAL framework and recommendations for new surgical procedures. [61**] Similarly, advances in immunosuppression have resulted in the latest penile transplantation performed in the USA needing very little toxic immunosuppression due to successfully induced immune tolerance. [4**] However, immunosuppression remains toxic and is, therefore, a significant barrier to successful long term penile transplantation.[62-64]

In contrast, dealing with a potential donor's family and the recipient has major psychological and societal risks involved, as elaborated in Table 1. [8;65;66] Informed consent for penile transplantation is difficult, in particular being able to ensure adequate understanding on the part of the participant about the various risks they will be taking on. However, the prolonged work-up leads to many opportunities for the participant to consider the risks and benefits and discuss these with the study staff and their own support network. [41] Phalloplasty has in line with Gillies' predictions [1] often produced suboptimal results. [46;47] Once informed consent is possible, it is acceptable for the recipient to exchange a portion of his quantity of life left for the quality of life he desires. [50] However, many safeguards have to be in place for informed consent to be correctly executed (Table 1).

Guidelines for penile transplantation

Guideline development is important as single principles cannot stand alone and overshadow other principles. Balance, judgment, and agreement, should be sought, as difficult as it may be to reach. [39;43*;51] Guideline development, which should be based on best evidence, is hampered as only limited numbers of cases have been performed so far, and few long-term data is available. [41;44;67] The most up to date guidelines are The Baltimore Penile Transplant Guidelines [38**]. This group performed the most complex penile transplant to date transplanting most of the penis, scrotum, and part of the abdominal wall to a male who suffered a severe injury after surviving an improvised explosive device (IED) explosion. [4**] They suggested four main domains for the ethical conduct of penile transplantation related to selection, consent and privacy, post-operative concerns, and institutional requirements. Guidelines are likely to evolve as more cases are performed, and longer-term follow-up documented.

Conclusion

Penile transplantation has manageable ethical risks - like other VCAs. Society is likely uninformed of the degree of suffering of potential penile allograft recipients. Different aspects of penile transplantation have diverse ethical risks. Currently, the treating physician is the key advocate for men suffering penile loss. Ongoing guideline development is an essential step in balancing ethical principles, as sound judgment is needed in every potential penile transplantation case.

Key points

- Penile transplantation has potentially excellent functional and cosmetic outcomes, but informed consent, cost, and general acceptance by society remain issues of dispute.
- Potential recipients are a vulnerable group and at risk of existential suffering, being ostracized, and social death.
- The view that penile transplantation is only life-enhancing and not life-saving is challenged.
- Guideline development, such as the Baltimore Criteria for Ethical Penile Transplant, is essential but hampered by only a few cases performed so far.

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Table 1. Ethical principles and benchmarks from Emanuel [40] applied to penile transplantation.

Principles from [40]	Benchmarks from [40]	Applied to penile transplantation (original)
Collaborative partnership	<p><i>“Develop partnerships with researchers, makers of health policies, and the community.</i></p> <p><i>Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the healthcare system.</i></p> <p><i>Respect the community’s values, culture, traditions, and social practices.</i></p> <p><i>Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.</i></p> <p><i>Ensure that recruited participants and communities receive benefits from the conduct and results of research.”</i></p>	<p>So far, collaboration with policymakers appears to be suboptimal as healthcare funding is still lacking worldwide, leading to very few penile transplants being performed. [2**3;4;5]</p> <p>Advocacy is needed to inform society about the suffering as well as the cost to communities in relation to other established healthcare services.</p> <p>The community’s values, cultures, and traditions in different parts of the world vary widely. This underscores the importance of investing in sincere community engagement ahead of and during penile transplant research to offset risk and to help towards shifting societal perception on the issue.</p> <p>Community leader interviews were helpful and done by the South African group prior to transplantation, confirming sympathy and positive attitudes towards penile transplantation. [5;41]</p>
Social value	<p><i>“Specify the beneficiaries of the research—who.</i></p> <p><i>Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries—what.</i></p>	<p>The beneficiaries must be the patients and the community through increased levels of care for similar cases. In general, cases will be few. Cases will increase during military conflict and ritual circumcision season. [17;20;42]</p>

	<p><i>Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements. Prevent supplanting the extant health system infrastructure and services.”</i></p>	<p>Some of the principal objections against penile transplantation are costs. [9;10] While researchers and other institutional role-players should strive to make penile transplantation as cost-effective as possible, the actual cost of penile transplants should not be more than the cost of renal transplantation. [43*]</p> <p>In addition, due to its small select target population, penile transplant is unlikely to be performed frequently enough to pose a significant economic burden. [38**;43*]</p>
<p>Scientific validity</p>	<p><i>“Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research.</i></p> <p><i>Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the healthcare interventions to which they are entitled.</i></p> <p><i>Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local healthcare and physical infrastructure.”</i></p>	<p>The design of penile transplant protocols/guidelines- it should adhere to and learn from other VCA protocols/guidelines. [38**]</p> <p>Suboptimal scientific research is unethical. [40]</p> <p>Facilities, where penile transplantation is performed, should have sufficient knowledge and a culture of organ transplantation as well as microsurgical vascularized free flap tissue transfer techniques. [44]</p> <p>New surgical techniques should follow the Idea, Development, Exploration, Assessment, Long-term study format (IDEAL) – this is only possible in formal research settings. [45]</p>
<p>Fair selection of study population</p>	<p><i>“Select the study population to ensure scientific validity of the research.</i></p> <p><i>Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.</i></p>	<p>Penile transplant is currently only to be performed for adults who lost their penis from trauma or cancer and are not willing to consider phalloplasty due to the known inferior outcomes. [46;47] Psychological assessment is vital for</p>

	<p><i>Identify and protect vulnerable populations.”</i></p>	<p>fair selection of recipients towards risk minimization. [28;41;48**] Indications may, after sufficient, review be expanded to severe degrees of microphallus and epispadias. Gender affirmation penile transplant and penile transplantation in congenital aphallia require more complex surgery; more research on the surgical technique and psychological impact on this patient group is needed in addition to the cadaver study that proposed a feasible surgical technique. [49**]</p>
<p>Favorable risk-benefit ratio</p>	<p><i>“Assess the potential risks and benefits of the research to the study population in the context of its health risks. Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.”</i></p>	<p>The risk-benefit ratio may be judged differently from the patient’s and the researcher’s perspectives; therefore, due care should be taken. [50] While assessment of the risk-benefit ratio remains a judgment decision that may be open to different interpretations [51], there are some key considerations that should form part of any risk-benefit analysis. Overall, the value of improved quality of life, both physically (e.g., improved urination, sexual function, appearance) and psychologically (e.g., self-confidence, sense of self), needs to be balanced against the risks posed by the surgery and lifelong immunosuppression. [38**] While it is possible to be “normal” again [4], immunosuppression that should be taken meticulously for a lifetime holds potential lethal complications despite modern advances. [52*;53] While in well-selected cases, psychological recovery is expected to follow normalization in appearance and function, the risk of “psychological rejection” remains. [6;7] Patients should be screened to ensure they are both physically and psychologically</p>

		suitable towards risk minimisation and long-term adherence to the immunosuppressive regimen. [38]
Independent review	<p><i>“Ensure public accountability through reviews mandated by laws and regulations.</i></p> <p><i>Ensure public accountability through transparency and reviews by other international and non-governmental bodies, as appropriate.</i></p> <p><i>Ensure independence and competence of the reviews.”</i></p>	<p>New penile transplant programs have to obtain governmental approval to transplant new types of tissue. [41]</p> <p>IRBs with public representation and competent reviewers should review the protocols. [16;38**;44]</p> <p>The limitations of IRBs to scientifically and objectively review innovative VCA (such as penile transplant) should be recognized by IRBs. [16] The South African team benefitted from having an ethicist as a team member and closely and transparently working with the IRB. [5;41]</p>
Informed consent	<p><i>“Involve the community in establishing recruitment procedures and incentives.</i></p> <p><i>Disclose information in culturally and linguistically appropriate formats.</i></p> <p><i>Implement supplementary community and familial consent procedures where culturally appropriate.</i></p> <p><i>Obtain consent in culturally and linguistically appropriate formats.</i></p> <p><i>Ensure the freedom to refuse or withdraw.”</i></p>	<p>Patient autonomy and a full understanding of the risks and benefits allow patients to choose penile transplantation as a therapeutic option. [38**;50;54]</p> <p>Due to the time spent in the work-up phase for penile transplantation, there is ample time for potential recipients to assess the risks and benefits. These risks should be communicated frequently to patients with open communication channels and a safe space for questions to ensure informed consent. [41]</p> <p>Patients should have the option to withdraw from the study even after transplantation and should, in these cases, be offered phalloplasty. [38**;41]</p>

<p>Respect for participants and communities</p>	<p><i>“Develop and implement procedures to protect the confidentiality of recruited and enrolled participants. Ensure that participants know they can withdraw without penalty. Provide enrolled participants with information that arises in the course of the research study.</i></p> <p><i>Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants’ at least as good as existing local norms.</i></p> <p><i>Inform participants and the study community of the results of the research.”</i></p>	<p>The study participant is not only the recipient but also the donor and the donor family who should be treated with the appropriate degree of sensitivity. The donor should be offered an abdominal skin flap phallus to retain dignity and prevent emasculation. [5;41] While concerns for confidentiality exist in the context of media interest [38**;41;44] media were thus far very respectful and did not search for or revealed the identity of the recipients who did not want to be identified. Respecting anonymity is vital towards the prevention of stigma and likely discrimination that participants might suffer if their identities were revealed. [22;25]</p>
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CHAPTER 5

Living with someone else's penis: The lived experiences of two South African penile allograft recipients

This chapter consists of a publication-ready manuscript in which we discuss the experiences of the two transplant recipients using qualitative research methodology. The manuscript was formatted in accordance with the 'instructions for authors' for the *Journal of Social Science and Medicine*.

Living with someone else's penis: The lived experiences of two South African penile allograft recipients

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Living with someone else's penis: The lived experiences of two South African penile allograft recipients

Abstract

Background

In South Africa, penile loss is a recognised complication of ritual circumcision, which has a profoundly negative effect on these men's psyches and their everyday lives.

Aim

The purpose of this paper was to investigate the experiences of the first two South African penile allograft transplantation recipients in order to assess the psychosocial impact of this surgery.

Methods

A qualitative descriptive phenomenological approach was used. A total of four in-depth interviews were conducted with the two South African penile transplant recipients. The interviews were transcribed verbatim while adding the field and observational notes. Thematic analysis was used to derive meaning from the collected data.

Outcomes

The interviews focused on the participants' lived experiences of ritual circumcision, penile loss, and undergoing penile transplantation and how it impacted their psychological wellbeing, interpersonal relationships, and everyday lives.

Results

After the penile loss, both participants reported feeling suicidal for the following reasons: their communities shunned them and regarded them as 'dead,' they felt severely ashamed of their disfigured bodies, they were unable to develop intimate relationships and could not have children. Transplantation gave them a fully functional penis, which resolved the majority of these issues. The participants were able to build relationships and satisfy their own and their partners' sexual and relationship needs. The transplant led to the complete restoration of their self-image and manhood. They were, however, still persecuted by their traditional communities as they had not successfully completed the ritual circumcision ceremony.

Clinical Implications

The information obtained from the interviews is important to take into account when considering to offer this surgery to other patients.

Strengths and Limitations

The limitations of the study are the small sample size and recall bias due to the relatively long period since the transplantations. Despite these limitations, the study finds strength in the novelty of the research topic. The participants had a unique story to share, and this study provides the first in-depth account of how penis transplants impact the lives of the recipients.

Conclusion

This study emphasises the necessity of offering penile transplantation as a treatment for penile loss as this is not only life-enhancing but lifesaving, especially within the South African context.

Keywords: penile transplantation, allotransplantation, vascular composite allograft, ritual circumcision

Introduction

Complete or partial penile loss are recognised complications of ritual circumcision in South Africa, with some 250 men suffering this fate each year;¹ beside penile loss, this ritual also carries a real mortality risk. Penile loss is to cultural purists an indication of weakness and has a significant impact on how these men are perceived by their communities. They are ostracised and are not regarded as 'men' in the traditional environment where they are treated as 'boys' by men younger than themselves; this is because they failed to complete the ritual circumcision and are left without a functioning penis. While they are perceived as boys, they are treated as if 'dead' and not worth including in the affairs of the community. Seeking assistance from Western medicine is considered taboo, adding to the profound impact of penile loss on the psyches of these men.^{2,3}

The penis is symbolic of masculinity and manhood. It is also an essential organ for sexual pleasure and reproduction.⁴ Maslow's hierarchy of needs is a theory that depicts the basic needs of an individual that should be met in order for that person to reach

self-actualisation, that is to become the most that he or she can be. These needs are depicted as hierarchical levels with the lowest (and most important) being deficiency needs. The deficiency needs are physiological (food, shelter, sex and reproduction), safety (stability, employment and health), love/belongingness (intimacy, family, sense of connection and being part of a group) and esteem (respect, self-esteem, status, recognition, strength and freedom). The higher-order needs are known as growth needs and entail cognitive and aesthetic needs, self-actualisation and transcendence. This theory states that individuals need to meet deficiency needs in order to be motivated to fulfil growth needs with the end goal of reaching self-actualisation and transcendence.^{5,6} For men who are aphallic, many of the basic needs remain unmet. These needs include physiological (e.g. health and sex), safety, love and belongingness (e.g. building intimate relationships and being accepted by the community), esteem (e.g. self-esteem and respect) and self-actualisation needs. According to Maslow, an individual who does not have these basic needs met will be at increased risk of psychological morbidity as the person will find it extremely difficult to lead a fulfilled life.⁷

Penile loss has been reported to have devastating effects on the psychological state of affected individuals. Studies focusing on the impact of penile amputation after penile cancer have found quantifiable mental illnesses, especially related to feelings of hopelessness, as well as high suicide rates amongst these patients.^{8,9} A Norwegian quality-of-life study reported that seven out of thirty patients treated with penile amputation for penile cancer would have preferred a less morbid procedure preserving sexual function even if it meant a reduced lifespan.⁹ Significant numbers of severe genital injuries occur in combat. In the Iraqi war, 147 men lost their entire penis and at least one testicle mostly due to blast injuries.¹⁰ As the loss of a penis or other genitalia is associated with a traumatic life event, it often leads to posttraumatic stress disorder. This makes recovery of sexual function more difficult and complex.^{11,12}

Social death,¹³ referring to severe psychological withdrawal related to, amongst other things, ostracism¹⁴ and existential suffering, is highly likely present in these men before penile transplantation. Therefore, the question arises whether penile transplantation can reverse this. Existential suffering, as defined by Kissane, refers to the impact of an advanced medical condition (such as penile amputation) on the individual's life

experience and reason for existence.^{13,15} Enforced ostracism, as seen in South African men after penile loss, has been labelled 'the kiss of social death'.¹⁶

The conventional treatment for penile loss would be reconstructive surgery using own donor tissue such as a forearm fascio-cutaneous flap. Erections for this flap are created by the insertion of a penile prosthesis. While good results are achieved in many cases, complications remain common; these include urethral breakdown and fistulation, flap atrophy that prevents prosthesis insertion, phallic hair growth and prosthesis failure or extrusion. Donor site morbidity is also significant.¹⁷ As previously discussed by Van der Merwe et al., the capital cost of a penile prosthesis approximates US\$7 330 and there is a relatively high expected complication rate in this patient group, which makes this a less desirable option in the South African context.¹⁸ Although tissue engineering of the penis should be possible one day, current projects to attempt this have been unsuccessful.¹⁹

To our knowledge, no studies that describe the impact of penile loss and penile transplantation from the patient's perspective have been conducted to date. Therefore, the current study is aimed at providing a detailed description of the lived experiences of the two South African adult recipients of penile allografts for the treatment of penile loss due to complications related to ritual circumcision. The purpose of sharing these participants' stories is to illustrate the impact that this procedure had on the lives of these men and to argue that this surgery is life-enhancing as well as lifesaving.

Materials and Methods

Approach

A qualitative descriptive phenomenological approach was selected as it allowed the researchers to gain in-depth insight into the phenomena under investigation from the patients' perspective. This was preferred over a quantitative/quality-of-life approach, which would have reduced their experiences to figures and numbers. Maslow's expanded hierarchy of needs as well as the theory of existential suffering as described by Kissane provided the theoretical framework.¹⁵

Procedure

The only two patients who had undergone penile transplant surgery in South Africa were purposively selected and approached by the first author (AVDM) for participation.

AVDM was the lead surgeon of a team of surgeons who performed the surgery. During a routine follow-up visit, AVDM informed each patient of the aims and objectives of the study and invited him to participate. Both agreed and signed consent forms approved by our Human Research Ethics Committee. They were subsequently contacted by an independent male researcher (YT) to schedule a suitable date and time for the interviews.

YT was selected to conduct the interviews in order to avoid a power differential effect, since he was not involved in the participants' medical management. He had also had no prior contact with them and was an experienced qualitative researcher with a background in circumcision experiences.

The interviews were conducted in a private room at the hospital on a day that the participants had a routine follow-up visit scheduled. YT was the only person present during the interviews. He gained permission to audio-record the interviews, introduced himself, gave a brief background of his research experience and explained the purpose of the study. The initial interviews were conducted over one day per participant and were divided into two sessions of about four hours each. A topic guide, designed by all the authors, was used to guide the conversation. This consisted of open-ended questions that focused on the participants' lived experiences of ritual circumcision, penile loss and undergoing penile transplantation and how it impacted their psychological wellbeing, interpersonal relationships and everyday lives. Both participants were contacted for a telephone interview of 20 to 30 minutes to clarify further and to add depth to their responses in their initial interviews. All interviews were conducted in English, although the participants were given the option to speak in their mother tongue (isiXhosa), which would have been transcribed by a translator later.

The participants also permitted the use of their hospital records to provide further context for the collected data. AVDM and YT furthermore made observational notes about the participants' body language and demeanour during routine hospital visits and interviews. AVDM is an experienced surgeon and principal investigator of the main penile transplant study who has been involved in the process of offering penile transplants since 2009. Therefore, he provided further context to the data from his own experiences and informal conversations that he had had with community leaders, men who had experienced penile loss as well as the recipients. Data collection ceased once

the researchers believed that they had collected sufficient in-depth data on each of the cases. As there were only two suitable participants, data saturation was not reached. Additional findings are expected to emerge as more men who have undergone this surgery are interviewed in the future.

The interviews were transcribed verbatim by YT, and observational data were added where appropriate. The data were analysed using descriptive thematic analysis. Three authors (AVDM, YT and CS) independently open-coded the transcripts for themes using deductive and inductive methods. Themes were initially pooled around the study objectives to give a detailed description of life before and after penile transplantation. Specific emphasis was placed on how the surgery assisted the individuals in overcoming the existential challenges faced by the penile loss and how they were able to fulfil their basic human needs. The validity of the data was ensured by involving coresearchers in the analysis process. The findings were reported back to the participants for comments to ensure that the data were accurately presented. Atlas.ti7 software (ATLAS.ti, Scientific Software Development, GmbH, Berlin) was used to assist with data management and the coding process. The procedure followed is consistent with the Consolidated Criteria for Reporting Qualitative Research checklist.²⁰

Ethical approval for this study was granted by the Human Research Ethics Committee of our institution. Informed consent was obtained before data collection. No identifying data were collected, and the aliases 'Thulani' and 'Sipho' were adopted and used throughout the study. This was a vulnerable group, and care was taken to maintain confidentiality at all times. There was a concern that they might be identified by close friends or family as currently there are only two cases. The participants were made aware that psychological support would be available if needed.

Results

Sample description

Thulani and Sipho are 43- and 26-year-old Xhosa males. Both believe in the Xhosa tradition of ritual circumcision. They described being excited and motivated to undergo ritual circumcision as this would have changed their status within their traditional community from a 'boy' (as all uncircumcised males of all ages are called) to a 'man.' Thulani and Sipho attended circumcision school at the ages of 22 and 19 years

respectively; the catastrophic result for both was total penile necrosis, which rendered them aphallic. Siphso received a penile allograft in 2014, two years after the penile loss. Thulani waited 18 years before he received a penile allograft in 2017.

Siphso was interviewed five years and Thulani about two years after the allotransplants. Despite being interviewed years afterwards, both men became emotional when recalling the traditional circumcision event that changed their lives so dramatically; neither participant successfully completed the circumcision ritual. As a result, they were persecuted and ostracised by their communities. They were reluctant to talk about their ordeal as they feared that they would be harmed by cultural purists. They refrained from using public spaces, especially restrooms, as they had to sit when urinating. As a result, they became socially isolated and both decided to relocate.

Siphso had supportive sisters and relocated to a different province to live with them. Thulani did not have the same level of support and experienced rejection from his family. His brother had been the person who was designated to ensure his wellbeing during circumcision school; he partly blames his brother for what happened. Thulani already had a strained relationship with his father that was further tested by the ordeal; he therefore did not have the needed support from his family to deal with his trauma. He decided to protect his secret at all costs and isolated himself socially. He dropped out of school and started moving around South Africa to avoid building close relationships. He chose areas that had few resident Xhosa individuals and relocated as soon as a Xhosa person moved in. He felt that this was necessary because, in their culture, it is completely acceptable to ask members to prove a successful circumcision by a show of genitalia. A ritual circumcision leaves a typical scar that appears different from the fine surgical suture line of medical circumcision. As a result of their relocation and psychological distress, both men were unable to maintain a steady job, build a career or maintain the friendships that they had before the circumcision. They also failed to forge strong new friendships.

Thulani had an understanding and supportive intimate partner before losing his penis. Their relationship lasted for a few years after the loss before he felt he had to 'let her go' because he could not satisfy her sexual needs or father children. Subsequently, he was unable to form other meaningful relationships; he would be in a relationship for a short period and then fabricate excuses to break the friendship before the relationship

became sexual. Siphos ended the relationship that he was in shortly after returning from circumcision school which left him aphallic. He did this as he did not feel that this relationship was serious enough to justify sharing this sensitive information. After this relationship, he struggled to maintain new relationships. He did, however, start dating a woman shortly before having the penile transplant in 2014. Thulani describes the period between losing his penis and receiving the transplant as a devastating and depressing period. Siphos shared this sentiment and added that he would prefer to forget about it again as the problem had been resolved.

During informed consent for the transplant, both were informed of the risks of immunosuppression and were offered phalloplasty. In public hospitals in South Africa, penile prosthesis is not an option due to the cost.

Themes

Penile transplant surgery and recovery

Both men declined phalloplasty as they felt that the only viable solution for them would be a 'real penis.' Thulani explained as follows after being offered phalloplasty by a plastic surgeon: "I said, no Prof, if this is what he is offering, then I am sorry. I still want sex, I still want kids and what he is offering me is not going to give me those things, so let's just forget about it. And as I was about to leave, a certain doctor told me: listen, there is a Professor [academic hospital], he is doing this kind of research about doing a penis transplant. It's going to be fully functional, but I am going to be on medication for the rest of my life. A medication that might result in a cancer in about ten years' time. And I told him that I will make two babies before I develop the cancer."

Both Thulani and Siphos successfully received penile allotransplants. They were initially in disbelief that it had happened and were therefore both anxious and excited to see what their penis new looked like. During the first removal of bandages, Siphos exclaimed, "I want to see my penis!" After seeing it, he fell backwards in the bed with tears in his eyes and was silent for a few minutes. He was elated with the results and described feeling 'number one'. Thulani, however, was not pleased by what he initially saw. When asked to elaborate, he explained, "Because it was swollen and scary with all the stitches, and I was like: My God, what kind of a penis is this? [BOTH LAUGH] As time went on, it improved."

After surgery, Siphon and Thulani remained in the hospital for a month. The penises gained full function, and at three weeks, they were experiencing unpleasantly painful erections as the scars were still healing. They were prescribed immunosuppressive medication that had some bothersome side effects. Each had to take a large number of tablets every day, and frequent hospital visits were required. Multiple blood samples were taken to assess blood levels to establish the correct drug dosages and monitor for adverse effects. Both participants had skin rashes. Siphon also had swelling in his extremities due to a serious fungal infection. These side effects seemed to bother Siphon more as he was a competitive bodybuilder. He stopped taking his medication about two years and eight months after surgery as the skin rash negatively affected the outcome of the competitions. He lost about half of his allograft before transplant rejection was successfully reversed, but he had to have skin grafts.

Despite these complications and the need for chronic medication, the participants expressed gratitude for the penile allograft. Even though both participants struggled with taking the medication initially, it became part of their daily routine. They will happily continue taking their medication, despite the potential side effects, as the alternative is worse. They do not ever want to go through the trauma of losing their penis again. Thulani stated, "Yes, at first, it [taking the medication] was a bit difficult because I wasn't used to, but for me that is the easiest part. You see, because this is something I am not willing to lose. Not again. So if I want to keep this, then I must continue enjoying my meds."

Living with someone else's penis

Thulani received a circumcised donor penis that was a poor skin colour match. However, this did not seem to be an issue for him: "They told me before the operation that the donor was a white person and was I going to be comfortable with the donor being a white person? I told the sister: Sister, I want a penis. That's what I want and I am not going to take my pants off and run all over [township] to show them my penis. So I don't care if it is white, or it's pink or purple. Prof knows, I said to him that ... I will settle for anything." Life without a functional penis was devastating to the degree that he was content with whatever colour penis he was given, provided that it was functional.

The offer was made to Thulani to have the graft penis tattooed to match his skin colour, to which he responded, "I don't know if I'm okay with it, I'm so used to this one, it will take some time to get used to a new one [LAUGHING]. I was talking to a friend and I said to him: You must not think we are the same? Why not? ... I'm special and you are not. And he was like what makes you so special? I said that I am the only Black man in the whole wide world with a white [man's] penis. [BOTH LAUGH] So yeah, but one of the other reasons we decided not to dye it was that Prof was afraid that I would get an infection." Thulani has fully accepted his penis and feels that it is something that makes him unique. He has also found a way of explaining it to a female partner or if anyone asks by telling the person that he has vitiligo, a common skin disease amongst black South Africans.

In contrast, Siphon received an uncircumcised donor penis that was a good colour match. For this reason, he feels that it looks similar to the one he lost. He is also not bothered about what it looks like as, once again, the functionality of the penis is more important.

Both participants admitted to sometimes being aware that they have someone else's penis attached to their bodies, but then they quickly remind themselves that it is now theirs and part of their body. Thulani further rationalised that the donor had died and had no further use for his penis.

Reintegration into society

Both recipients described feeling less socially isolated and more confident after the transplant. They felt more comfortable in social spaces and were able to build new friendships. They were able to use public restrooms again without the fear of people finding out what had happened as they were able to urinate standing. This was more so for Siphon as he had received a penis that was a good colour match. If questions were going to be asked about their penises, they had good cover stories in place.

The participants emphasised that they had been 'brought back to life' by undergoing transplantation. Siphon explained that he had chosen to have this surgery as he 'chose life'. In the Xhosa culture, aphallic circumcision failures are seen as 'dead' as they cannot perform their 'duties'. These findings were obtained from a community leader interview in 2011 during which AVDM also heard that giving "these men" a penis would

be like "bringing them back to life as they are seen as dead". Thulani and Sipho felt that by having this surgery, they were able to reintegrate into their social communities; however, full acceptance by their Xhosa peers was not as simple. Thulani explained, "At some point I thought, okay, if we do this transplant and it works, people would look at things differently and see a second chance, not only for me but for others too, you know? But then again, it's not happening ... Of which is something I told myself that I wasn't going to bother myself much with. Because ... at the end of the day, it's not about people and their negative thoughts, it's about me and I have made peace with the fact that they will never fully accept us."

If found out, these men will still be seen as 'boys' and will not be accepted by the community and will be ostracised again. As a result, they remain fearful of disclosing what has happened. Despite this persecution, the participants appreciated having a functional penis and decided to rather focus on the inner peace that they had found and the positive impact that the transplants had on their personal lives.

Intimacy and sex

Both participants described a vast improvement in their ability to have intimate relationships and were excited to be having sexual intercourse again. Thulani explained, "I was told not to rush things. You know, wait for it to heal properly before I can go and paint my areas sexually. [LAUGHS] So yeah, that's what I did, and I was excited. That's one feeling I would never forget [having sex again]." After many years of avoiding relationships, Thulani successfully entered into a sexual relationship shortly after his transplantation. They dated for a few years before the relationship ended. He described being confident in his ability to satisfy his partner's needs.

Sipho remained single after his penile loss. He entered a heterosexual relationship shortly before having the penis allotransplant. He described his girlfriend as being very understanding of his situation. He did, however, feel the need to have sex with her as soon as he recovered from surgery. "Yes and then after I was going out [discharged, five weeks after the penis transplant] ... the same day I was do the sex." They ended the relationship after their child was stillborn at term. Sipho became promiscuous, having sex multiple times per day and having multiple sexual partners. Despite advice to use condoms, Sipho contracted urethritis that was treated successfully.

Both participants described the sensations during sex as being the same as with their native organs. Both participants felt that this was a major positive aspect of receiving a penis transplant as they were able to enjoy something that they had been deprived of for many years. For them, it was not only about the sexual act but also about their ability to build lasting relationships, which is a necessity when trying to lead a fulfilled life. Regaining their normal sexual function seemed to have spearheaded their psychosocial recovery and has led to a major positive change in their mood and wellbeing.

Restoration of self-image

The penile loss had devastating effects on both participants' psychological state, especially with regard to self-esteem and identity. They described feeling severely depressed and at times harbouring suicidal thoughts. As they had lost the essence of their manhood, they felt cast out, worthless and ashamed. Thulani found it difficult to look at himself in the mirror and see his maimed body. At times, he did not wash the lower part of his body as it was emotionally too painful. He resorted to heavy drinking as a coping mechanism. Post surgery, he felt like a different person and looking at his lower body was more pleasing. When asked what it meant to receive a penile transplant, Siphso responded, "It is good to be a man again!" Both appreciated the restoration of their feeling of manhood. They now put effort into their grooming, dress smartly and seem more confident and happier since the transplant.

The participants described that the transplant had given them hope and motivated them to lead a more meaningful life. It enabled them to pursue life goals that they had previously neglected. An important aspect of leading a meaningful life that was restored was their ability to reproduce. Having children is important for Xhosa families as their wealth is measured by the number of children that they have. Siphso explained, "Yes it changed my life, because of if I didn't get the penis back maybe I don't [have children], we want our children." Siphso impregnated his girlfriend in the first year after the transplant; unfortunately, she delivered a stillborn term baby. Thulani felt that not being able to have children was one of the biggest losses that he experienced after having a penile amputation. His hope to have children has now been restored.

Both participants stated that they would accept the transplant again if they had to, due to the positive impact that it had on their lives. Thulani explained, "It made me look at

life differently. For instance, there were times where I didn't see a point in living, you know? But now I see myself as being lucky that I'm still here ... and alive [not committing suicide]. Because there are people who did not get the chance. I still want to live some more.... There are certain things I still want to do. Some are new things, and some are things I have always wanted to do. I look at life with a more positive eye. Because at first, there was no point, REALLY.... I've grown a little bit and I still want to grow some more. I wish I can help where I can. The reason for that is that I also want to change lives. I mean, I got lucky. I met people who managed to change mine. For instance, one of the positive things ... I used to drink heavily ... That's why I am saying that I look at life differently, you know? I sort of look at the bigger picture. The blinkers that were there before are no longer there. I look around and I look at the possibilities." (Preoperative psychiatric evaluation confirmed that the drinking problem was an attempt at coping and suggested that a penile transplant might be curative.)

Discussion

Qualitative data in vascularised composite tissue allotransplantation are sparse. Herrington, reporting on five hand transplant cases, found a great improvement in patients' overall health and recommended that a qualitative component be added to all such cases.²¹ Our qualitative study provides an interesting insight into the real-life experience of two men who received a penile transplant. Receiving a penile transplant was experienced as daunting but exciting at the same time.

At first sight, the penis was not entirely what was expected for Thulani but after the recovery period, the penis was aesthetically pleasing and fully met the expectations of the recipients. They accepted and integrated the organ fully as their own. This is in contrast with a previous case reported from China where a penile transplant was attempted in 2005. The transplanted penis had to be removed in the early postoperative period due to 'psychological rejection.' Photographs of the Chinese transplant showed a partially necrotic-appearing penis. This might have added to the psychological rejection.^{22,23}

Psychological rejection in renal and cardiac transplantation is well described and might relate to the altered self-image with the introjection of a new organ. It is postulated that the self-image becomes fluid again and that the inserted organ causes a ripple effect on the self-image that might even induce psychosis.^{24,25} The reason our two cases and

the two successful American cases^{26,27} have not shown psychological rejection might relate to careful case selection, adequate psychological preparation preoperatively, the small sample size or perhaps the relief of existential suffering and 'social death'. Existential suffering and social death were likely present due to the circumstances of the ostracised recipients who feared for their lives before the penile transplant.

Major forms of existential suffering that are prevalent amongst individuals who have a failed ritual circumcision include death anxiety, major change, loss of control, fundamental aloneness and altered quality of relationships. The rejection and ostracism experienced from their traditional communities, losing their partners and in Thulani's case losing his family support likely enhanced their existential suffering and their social death. This might have created a strong enough need to overshadow the potential psychological rejection of the transplanted organ.¹⁵

Before transplantation, social death was most likely present in both recipients. While both our cases were (and to a lesser degree still are) in physical danger from cultural purists as they 'failed the custom', they were most likely suffering from the psychological form of social death before receiving their transplants. While the medical form of social death is irreversible, the social science model is a reversible multifaceted one, comprising social isolation, loneliness, ostracism, change in personhood, change in role and identity, harm and disfigurement.¹³

Psychological social death and existential suffering in the absence of psychological support are likely to have induced the suicidal thoughts in both participants. In contrast, with the two American cases, less shame and more support were present before their penile transplants.^{26,27} In the first case, the recipient lost his penis after penile cancer surgery; there was no shame in that. The second case was a war veteran who lost his penis and part of his scrotum and lower abdomen after a blast injury in the line of duty. He would always be respected as an American hero and be completely accepted by his community while aphallic. Compare this to the South African context where the penises were transplanted in the utmost secrecy, the hospital allocated fake names and the staff was trained to avoid possible media leaks to prevent cultural purists or the recipients' community from harming them. Until now, the participants have both refused any type of media interview and insisted that the recordings of the interviews for this study be deleted to ensure confidentiality.

The penile transplants led not only to a physical transformation but also to an improvement in the recipients' psyches. Their self-worth was restored, and they were 'brought back to life' from social death. Therefore, by choosing to have penile transplantation and all that it involved, as explained during the informed consent process, they actively "chose life", in the words of Sipho. Penile transplantation allowed them to become 'men' again as they were transformed from being aphyallic to phallic. This led to a physical transformation as their bodies seemed whole again. They were given back their symbol of manhood and could once again look at themselves with pride. Their confidence was restored, which was evident in their change of demeanour and appearance. After their self-worth had been restored, the men were able to become more active members of their new communities. They refused to hide anymore, despite the danger of not being accepted by their traditional community should they be found out. They felt more comfortable in public as the presence of a penis and not having to sit down to urinate made it easier to hide their failed ritual circumcision. Interestingly, after the period of immunological rejection and partial loss of Sipho's penis, the penis has the appearance of being partially mutilated by ritual circumcision, giving credence to his cover story. Thulani has a circumcised transplanted Caucasian penis and informs anyone who asks that he is suffering from vitiligo that started in the genitalia.

Both participants were able to maintain new long-term relationships and regained their full sexual function with erection-enhancing oral medication not needed by Sipho and occasionally needed by Thulani towards the end of 2019. They were able to satisfy their own sexual needs as well as those of their partners, describing sexual intercourse as being as pleasurable as before their penile loss. In earlier interviews, Sipho had claimed that he was sexually active up to or more than five times per day over weekends. It is unlikely that the same result would be achieved by skin flap phalloplasty and an inflatable prosthesis, which might extrude at these high levels of sexual activity. The identity restoration of these men may be compared to the experiences of women receiving breast reconstruction after mastectomy for cancer to restore their womanhood and their sexual desirability.²⁸ Losing an organ unique to a man or a woman has a devastating impact on individuals' sexual identity, and restoring their disfigured bodies restores their gender identity and their self-confidence; it facilitates

acceptance by their communities and aids in building relationships. This is essential for living healthy, meaningful and fulfilled lives.

Regaining a penis restored Sipho's and Thulani's sense of 'self'. They regained most of the self-identity that they had had before their ritual circumcision ordeal. It also assisted them in regaining a positive outlook on life. They seemed to be more positive about their futures and felt more confident in trying to build a proper career for themselves to better provide for their future partner and children. They described wanting to live life to the fullest and to try all the things that they were previously unable to do. This experience is similar to that reported by heart, liver and kidney transplant recipients for whom potential existential suffering was reversed.^{29,30}

An important outcome for the recipients was that the transplants enabled them to have children. Even though only Sipho impregnated his partner, the potential for having children is very important to Thulani as well. This is interesting as during the counselling process of informed consent, they were informed of assisted reproduction that would enable them to have children should they not have a penile transplant. Assisted reproduction is expensive in South Africa as even state patients have to pay full private rates. This might have caused them to conclude that it was impossible for them due to the cost. Alternatively, 'selective hearing', often guarded against in an informed consent process of innovative treatments and vulnerable groups in life-or-death situations, might have accounted for this finding.³¹

From the evidence provided, it is clear that penile transplantation addressed many of the basic needs described at each level of the hierarchy proposed by Maslow.⁶ The respondents' physiological needs of sex and reproduction, safety needs of employment and stability and needs of love and belongingness were fulfilled, and their self-esteem was restored. As they were able to satisfy these needs, they now have the motivation to reach self-actualisation.

Despite the overall positive impact that the transplants had, it needs to be weighed against the recipients' need for lifelong immunosuppressants with potentially serious adverse effects. Despite this risk, they felt that they would gladly continue taking the medication as the alternative was being aphallic or having a phalloplasty.

The question remains whether phalloplasty with penile prosthesis would have produced similar results in terms of sexuality and restoration of the self but without the need for immunosuppression. The literature is scant on nontransgender male phalloplasty satisfaction reports. However, Callens et al³² investigated 18 males who had received phalloplasty; all cases had had multiple operations. Most respondents (10 out of 18) seemed sexually active at least via masturbation. However, 75% reported being inhibited in engaging in consensual sexual activity. Although 90% reported overall satisfaction, 50% were unhappy with the appearance of the genitalia. All five men in whom a urethral reconstruction had been attempted had fistulation, and three developed urethral strictures. Three out of five patients with attempted urethral reconstruction could stand to urinate. The men in the traumatic penile loss subgroup were the least satisfied with the results. Extrapolation of these reports from Belgium to Siphon and Thulani's context, where the penile prosthesis was not an option, is difficult. The drive behind penile transplantation in South Africa was to find a near-perfect, cost-effective solution for ritual circumcision-related penile loss that allowed restoration of the normal functions of the penis. As generic immunosuppression medication has become affordable, donor defects are avoided, sexual and psychological restoration results appear to be near perfect and the current side effects of immunosuppression do not seem to have a major effect on the two South African cases (and the two successful American cases), penile transplantation is probably the current gold standard for reconstructing major genital defects. However, in an informed consent process, phalloplasty should always be offered as this option excludes potential toxic immunosuppression.

The limitations of the study are the small sample size and recall bias due to the long period since the transplantations. In interviews that AVDM conducted with both participants early during the main study from 2011 to 2014, suicide was a more prominent theme than recently, even with prompting. We plan to do qualitative research on subjects who have lost their penis but have not had a penile transplant to gain further clarity on why this discrepancy was observed. The sensitive nature of the topic may have caused the participants to withhold certain details of their experience that may be too traumatic to share. Siphon was not as forthcoming with information despite both participants being offered the services of an interpreter. This could have caused a skewing of the information to a degree because most of the data arose from Thulani.

Despite these limitations, the study finds strength in the novelty of the research topic. The participants had a unique story to share, and this study provides the first in-depth account of how penis transplants impact the lives of the recipients. This is important information when offering this surgery to others.

Conclusions

Penile transplantation gave men in this case study a second chance at life with their sexuality restored. It had a positive impact on their psychological state, self-image and everyday life. Their manhood was restored, and they gained the confidence needed to reintegrate into society and to build meaningful intimate relationships. Hope was created to build a better future and to have children. They were not excessively troubled by having to use immunosuppressive medication. The study provides evidence that an emotional and social transformation occurred after receiving a new penis and that these men can meet the basic needs that all people aim to fulfil. The surgery is not only about allowing these men to have sex but also about restoring their self-esteem in order to give them the confidence to pursue self-actualisation and to lead meaningful lives. From their perspective, the surgery was lifesaving, not merely life-enhancing.

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List of abbreviations:

AVDM: Refers to the first author, Prof André van der Merwe

YT: Refers to co-author, Dr Yoesrie Toefy

CS: Refers to co-author, Dr Chantelle J Scott

CHAPTER 6

Penis transplantation: A review

This chapter consists of a manuscript invited by *Nature: Reviews in Urology* and is publication-ready. We discuss the current state of penile transplantation. We discuss the relevant anatomical and physiological aspects that make penis transplantation different from phalloplasty, as well as the psychological, ethical, immunological, and clinical matters associated with this type of surgery. The authors are from all the successful penile transplant centers in South Africa and the USA.

Penis transplantation: A review

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Abstract

Penile transplantation is the most recent addition to the range of vascular composite tissue allotransplantations (VCA), and to date, five have been performed in centers around the world. The functional and cosmetic results are highly satisfactory. However, the side effects of immunosuppression and donor shortages are likely to limit the number of penile transplantations performed. Phalloplasty, the current immunosuppression-free treatment for phallic loss, has drawbacks in appearance and function and has troublesome complication rates. Animal studies have contributed to the success of penile transplantation. Recent advances in immunosuppression minimisation strategies for VCA allows a reduction in side-effects. As penile transplants are not regarded as lifesaving by many, ethical matters arise due to the cost and potential complications of this procedure. The future of penile transplantation is possibly as part of genital transplantation in gender affirmation surgery. There are now several recent publications on penile transplantation. In this review, the individuals from the three centers at which penile transplantation was successfully performed

combine their experience to review the literature and summarise the current status of penile transplantation.

Introduction to penile transplantation

Penile transplantation is a novel form of vascular composite tissue allotransplantation (VCA). Five cases of penile transplantation have been performed since 2005.[1-5] The uniqueness of the procedure has generated considerable interest and criticism both from the lay public and scholars. Critics have labelled penis transplantation as unjustifiably costly and life-enhancing rather than lifesaving.

However, in most societies, the phallus is the very symbol of being a man, and being deprived of it robs the male of the essence of his virility and manhood[6]. In many cultures, the initiation of a boy to manhood involves the penis in the form of ritual circumcision. The penis is therefore vital in the rite of passage to adulthood. It has, through the ages, become embedded as a symbol of fertility, potency, and male sexuality in human cultures the world over.

Phallic symbols abound in ancient society emphasising the importance attached to the penis throughout the ages. Several ancient civilizations practiced phallic worship due to its inherent link to the survival of the human species. The worship of phallic gods or the phallus itself is recorded all over the ancient world in most cultures and many countries, including amongst the Hindus, Babylonians, Spanish, and English. Common ancient ithyphallic objects were obelisks and menhirs. Four thousand phalli were dug up around the Temple of Isis, a female god of fertility, at Paestum. Phallus worship also relates to the worship of masculine powers. The god Fricco in Upsala, Sweden, and the well-known Greek god Priapus is resembled with muscular strength and substantial size penises.[6]

In worship, the penis is linked to something as powerful as the sun based on 1. Mother earth is sterile without the sun; when the sun returns in the Springtime, food becomes abundant again. 2. The heat of sexual energy is linked to the sun's heat; extant phrases like 'burning desire' and 'steaming hot' derive from the heat of the sun. 3. With the rising of the sun in the morning, the penis seems to become 'awake,' and this is often the time when the act of procreation takes place. The need to procreate is one of the most

powerful forces in the universe. Without a penis, there is no possibility of procreation or ensuring the survival of the human species. [6]

In Chinese culture, the penis is seen as the life spring through which the generations flow. [7] Therefore, the loss of this organ can have a devastating effect on the transgenerational established psyche of the man, and the consequences of this should not be underestimated.

Replacing missing or damaged tissue with similar tissue, the 'like with like' principle has the best cosmetic and functional surgical outcomes and is one of the fundamental principles of plastic surgery espoused by Gillies. [8] Vascular composite allotransplantation (VCA), such as hand and face transplantation, consists of transplantation of various tissue components (skin, muscle, fat, blood vessels, nerves, and sometimes bone) and initially generated much controversy in terms of the associated psychological, ethical, and social aspects. In instances of complete loss of the penis, penile transplantation fulfills Gillies' principles, resulting in a successful restoration of the lost organ. (Figure 1).



Figure 1. The second penile transplant from South Africa at 22 months postoperatively. This represents a successful reconstructive outcome in line with Gillies' principles.

Causes of penile loss

The causes of and degree of penile loss are varied. The most frequently reported cause is ritual circumcision. [9] Some 250 severe penile mutilations or amputations are reported yearly from the Eastern Cape region of South Africa as a result of complications of ritual circumcisions. [10] Other causes of penile loss include combat-related injuries such as from improvised explosive devices (IED), high-velocity projectile injuries [11;12], electrocautery injuries in particular in children [13], self-mutilation, trauma, and traffic accidents [14]. An industrial accident caused the loss of the penis of the first attempt at penile transplantation.[2] Penile cancer managed with total penectomy led to the first penile transplant in the USA.[1]

Psychological considerations

Penis loss can negatively impact men in several ways, especially psychologically. Although controversial today, Sigmund Freud commented that 'anatomy is destiny.' He postulated that the presence of a penis and the ability to urinate standing in young children has a major role in gender identity and behaviour later on, as described by Moi. [15] The lack of penis may cause envy in girls; the discovery of the penis or lack of it in children is seen with similar gravity to the discovery of the inevitability of death. [15] In men who lost their penis, some form of regression is likely to happen, affecting the core of their self-image.

Penis loss can also impact men socially. In South Africa, a man who lost his penis after ritual circumcision is seen by the tribal community as "dead." [5] Social death refers to a multifaceted concept in individuals where the loss of identity, loneliness, loss of personhood, and ostracism is present. This has been identified in other VCA patients, such as hand and face transplantation. [16] While geographical cultural differences exist, social death is likely present in at least the South African cohort where ostracism after failing a rite of passage accompanies the loss of the penis. Ostracism has been labeled as the "kiss of social death." [17] The suffering in this group of men is so severe it might also be likened to existential suffering (end of life suffering from morbid conditions). [18]

There are fundamental differences in psychological responses related to the body image between transplantation surgery, where parts of the body are replaced, and other types of surgery where parts may be removed for various reasons such as

cancer. The body image is dynamic, has its own 'metabolism,' and is involved with a continuous interchange with the environment. [19] The frequency of postoperative psychosis is higher after transplantation than any other type of surgery. [20-22] In most cases, a transplant is a life-death situation for the recipient creating much anxiety. A penile transplant recipient has likely similar feelings due to the importance of the penis to the male.

The transplanted penis will immediately function as a new introject that must be accepted to be amalgamated into his body image or rejected, such as the first penile transplant in China that had to be removed due to 'psychological rejection' by the recipient. It is known that even a benign introject such as a cardiac pacemaker may have a psychological impact. [23] Challenging the ego with the addition of a new organ can cause anxiety that is more pronounced in borderline personalities. [19] It is therefore essential that all potential penile transplant recipients be screened carefully psychologically.

The recipient may want to identify the donor of the penis. By keeping the donor's identity anonymous, this issue may only partially be resolved as in fantasy, the recipient may still personalise the anonymous donor. This may induce feelings of indebtedness and guilt that might increase the difficulty of accepting the new penis as his own.[24] On the other hand, the immediate integration of the graft penis into the body image is possible. We were vigilant of potential integration difficulties during the first penile transplant in South Africa in 2014. [5] The patient immediately exclaimed at the first dressing change, "I want to see my penis," which indicated a good chance of positive integration.

Post-transplant sexual recovery may be complicated by post-traumatic stress - either from the events leading to the penile loss, such as ritual circumcision, penile cancer, or combat-related injuries or post-transplant stressors such as the psychological impact with added immunosuppressive medication side-effects. The penis, previously used for sexual intercourse and urination, was part of someone else's life, body image, and gender identity. It will now be used by a new "owner" for the same purposes with a different partner.

Althof et al. found that a single medical intervention alone or psychological treatment alone is not enough to restore sexuality where organic disease is present. Both are needed for recovery. [25] Penile transplantation, in conjunction with psychotherapy, has a major therapeutic role as it helps not only to restore organ function but also to heal a broken body image, severely reduced self-confidence, and manhood. A USA recipient said he is "normal" again [4], and a qualitative study on the two South African cases found that they see themselves as "alive again" (*unpublished data*). All cases received psychological support postoperatively. Overall, penile transplantation, in conjunction with psychological support, restores sexual ability, confidence, manhood, and urination in the standing position again.

Ethical considerations

Several reviews on ethical considerations in penile transplantation have been published and will only be briefly discussed here in the context of our experience performing penile transplants. [26-32]

Patients rendered aphallic are a vulnerable population, often discriminated against, and exposed to significant psychosocial suffering. This may result in their inability to grasp or internalise essential facts such as immunosuppression side effects and the need for life-long close follow-up that includes frequent blood tests. Informed consent is thus difficult. [27] Patients have the right of autonomy to trade portions of their quantity of life for the desired quality of life. [26] However, the potential recipient must fully understand the risks of surgical failure, rigorous lifetime follow-up in a transplant center, the lifetime dependence on medication to prevent rejection, and the myriad of potential side-effects of prolonged immunosuppression. As penile transplant workup is a lengthy process, the patient has the opportunity to consider alternatives such as phalloplasty, evaluate the risks involved, ask questions, be exposed to a transplant environment, and interact with other transplant recipients as well as the caring physician. [33]

While a good relationship between the treating surgeon and the patient is essential, pathological doctor-patient relationships are possible. For instance, an innovative alliance between the surgical team and patient may, unfortunately, result in consideration of risky treatment attempts to the detriment of the patient. Structured guidance on the ethical conduct of penile transplantation can avoid such conduct.

The development of guidelines based on available evidence is essential. [26;27;31] The recently reported Baltimore Criteria for ethical penile transplantation from the Johns Hopkins group is the most up to date and their context more relevant than other attempts as they performed the most complex penile transplant to date. [32] They argue that the difficult balance between the principles of conduct and virtues such as prudence, trust, compassion, and benevolence is possible with a carefully structured approach in a tertiary research setting. Their criteria revolve around 1. Selection, 2. Consent and privacy; 3. Postoperative concerns, and 4. Institutional requirements. They also consider the dilemma of pediatric penile transplantations, concluding it may not be ethical for parents to impose the risks of immunosuppression on their children. In these cases, it may be best to delay penile transplantation to early adulthood to allow recipient autonomy.

Animal models for penile transplantation

Animal studies have contributed substantially to our understanding of penile transplantation; the knowledge gained from these animal studies was critical to the success of human penile transplantation.

In 2003 Koga et al. tested a Brown-Norway rat total penis on adult 23 Lewis rat omental pouch transplant model using FK 506 as immunosuppression. In all the subjects, the harvested penis was wrapped in an omental pouch to gain blood supply. The authors reported that the omental vascularized graft could easily be moved to the pelvis on a pedicle of blood supply and concluded that this model might work in humans. [34] This study demonstrated that using a blood supply other than the natural blood supply to the penis could be successful. All four successful human attempts are based on this principle as the dorsal neurovascular complex in the recipients was deemed high-risk for thrombosis.

In 2005, Akyurek et al. [35] described a rodent model of 50 Sprague-Dawley adult rats for creating a vascular graft pedicle based on the internal pudendal artery and vein. This study confirmed that vascular supply other than the regular blood supply of the penis can be used and is associated with graft viability. They proposed that penile transplantation in humans should follow the same model.

Karamursel et al. described a similar rodent model in 2005. [36] They created six free penile flaps in Wistar albino rats. The flaps were created proximally at the origin of the corpora cavernosal and internal iliac/pudendal artery. The study confirmed the principle of using a different blood supply from the usual penile blood supply.

In a study using 24 Lewis rats, Sonmez and Siemionow (2009) reported that a technique of direct feeder artery-to-corpus spongiosum had excellent results. [37] This is a critical progression from the previous animal studies and an excellent future option to improve blood supply to more proximal penile transplants or total penile transplants.

Fidder et al. and Lough et al. (in 2019 and 2020, respectively) created rodent models for immunological experiments in penile transplantation. [38-40] Their models address the biggest challenge in penile transplantation: reducing the need for long term immunosuppression.

Zhao et al. (2016) devised a Beagle canine model of 30 dogs to compare ten pairs (20 dogs) and ten replanted penises. [41] Their model consisted of amputation and transplantation on the same blood vessels using microsurgical techniques similar to replantation. There was glans necrosis in eight out of the twenty (40%) transplanted dogs present. Although they thought the model could be utilized for human penis transplantation, the high rate of glans necrosis is concerning. The dorsal recipient arteries, as used in this model, are usually affected in humans by the pathology causing the original loss of the penis and should be avoided. [33]

Animal penile transplantation studies applied to human penile transplantation

The Chinese surgeons who performed the first penile transplant [2] anastomosed the recipient dorsal penile vascular system to perfuse the graft's corresponding vessels, similar to those used in Zhao's canine model for penile transplantation. [41] Although they reported adequate perfusion, the published picture of the graft at postoperative day 14 demonstrates significant discoloration; segmental epidermal necrosis of the penile shaft skin was reported on histology. [2;7] The four successful penile transplantations avoided the principles used in the canine model and applied the principles of the rodent models by using a blood supply other than dorsal penile vasculature. [1;3-5]

The high incidence of shaft skin necrosis observed after penile replantation is likely due to the inability to reconstitute the external pudendal blood supply. These findings suggest that the external pudendal vessels should also be used in the setting of proximal penile transplantation to prevent shaft skin necrosis. [42] In correlation with animal studies findings that external blood supply to the penis should be used, cadaveric studies by Tuffaha et al. stress the importance of utilizing multiple vascular pedicles to best perfuse the penile graft. [43]

The unique anatomy and physiology of the penis as related to penile transplantation and phalloplasty

While a complete review of the penile anatomy and physiology is not possible here, critical differences between a penis and the neo-phallus of phalloplasty exist and are presented here.

Penile skin has no hair or hair follicles. The hair in phalloplasty has to be managed with depilation to avoid unsightly hair growth. [44] Phalloplasty skin lacks the fine detailed texture and appearance of penile skin, which include a subtle pigment gradient that increases distally in the shrunken flaccid penile skin.

Langer describes skin "cleavage lines" (today known as Langer's lines) that appear to be parallel to the penis and are scanty. [45] Careful inspection of an uncircumcised penis reveals that the subtle skin creases run transversely in the penis much the same as the lines Langer described overlying a joint. These lines, in the case of a forearm fascio-cutaneous flap phalloplasty, would be longitudinal and cause the skin to differ slightly but visibly from penile skin in the flaccid and erectile state.

The lack of subcutaneous fat and hair follicles in the penis coupled with the elastic and supple skin covering the corpora creates a unique tactile feel and appearance. The skin is loose because the dartos fascia backing the skin is only lightly adherent to Buck's fascia. [46] In phalloplasty, the hairy fascio-cutaneous free-flap has subcutaneous fat densely adherent to the less elastic skin, creating a different tactile sensation to touch and visual appearance, even after depilation.

Skin necrosis and swelling post penis transplantation can be avoided by adequate arterial supply and venous drainage. The skin of the penile shaft, the surrounding

suprapubic, groin, and scrotal area, is perfused by the external pudendal vessels originating from the superficial femoral artery. [43] The dorsal arteries and veins of the penis derive from the internal pudendal artery. [47] and are drained by a greater saphenous vein.

The penis has a firmly attached root proximally and (mostly visible) body distally to be considered for transplantation. So far, only variable portions of the body of the penis have been transplanted and not the root. The penis root consists of the proximal crura of the corpora cavernosa attached to the junction between the perineal membrane and pubic rami and the bulb of the corpus spongiosum ventrally. [47] A possible function of this bulb may be to retain vaginal secretions during intercourse. The bulb is not currently replicated during phalloplasty. Transplanting the root as well as the body would be needed in cases of gender affirmation penile transplantation, severe blast injuries, and radical penectomy for penile cancer. This will pose more technical challenges than the penile transplantations performed so far – a possible technique is proposed in the 'Future directions' section below.

On cross-section, the body of the penis has a rounded but slightly triangular shape. The urethra and corpus spongiosum form the apex of the triangle ventrally, while the corpora cavernosa form the base dorsally. The corpora cavernosa has two collagen layers and intracavernosal collagen struts to help maintain rigidity during erections. When the corpus spongiosum (surrounding the urethra) is erect, the erection is softer ventrally as the tunica albuginea surrounding the corpus spongiosum has only one layer of collagen and no intra-spongiosal struts. [46] This creates a density gradient from ventral to dorsal that is not possible to effect in phalloplasty, where a rod-like appearance is more common after placing a single-cylinder prosthesis. Given that the interaction between the penis and the clitoris and vagina during intercourse is a delicate balance, [48] deviating from a 'normal' penis shape may negatively affect female orgasm.

Despite valid surgical efforts to create a glans penis at phalloplasty, this structure is possibly the most challenging part of the penis to recreate. The normal glans is composed of a different textured squamous epithelium than the skin of the neo-phallus. The erect glans penis provides a cushioning effect that protects the female genitalia

against the rigid corpora cavernosa. The glans also protects the corpora, which explains the mechanism of extrusion of penile prostheses in phalloplasty. Phalloplasty has a glans-like circumscribed appearance created by strategically placing coronal circumferential sutures over the distal phallus. The neo-glans is commonly composed of forearm skin. It is not possible to recreate the concave dorsal surface of a normal erect glans penis with the cone shape that assists intromission [49];. This cone shape relies on delicate longitudinal intra-glans collagen bundles. Interconnecting elastic fibers between collagen bundles create the particular shape, consistency, flexibility, distensibility, and rigidity of a normal flaccid and erect glans penis. [50]

The dorsal penile arteries perfuse the glans penis, shaft skin, and penile fascia. [47] The dorsal penile arteries also provide perfusion to the corpus spongiosum surrounding the urethra via the glans. This is important in penile body transplantations where the penis may have been retrieved distal to the bulbourethral arteries (also branches of the internal pudendal arteries). The deep penile arteries, also called the cavernosal arteries, provide the principal blood supply to the corpora needed for erections. However, they may not be crucial for erections as they do not exist in all males. [46] In the two South African penile transplants, they were incompletely reconstructed, and full erections were still possible. The small cavernosal arteries can be reconstituted by anastomosing them proximal to their origins, where the vessels are larger.

Phalloplasty does not appear or function physiologically as a normal penis. Kerckhof et al. found that 32% of trans men experience difficulties initiating and seeking sexual contact. [51] Furthermore, Kerckhof et al. report orgasmic difficulties, affecting 15% of trans males after phalloplasty, as one of the major concerns to patients. [51] This may possibly be explained by the difference in type and density of nerve receptors, which are located all over the glans penis. Nerve receptors are especially abundant at the distal inner part of the foreskin and the coronal sulcus. These nerve endings, including Meissner's corpuscles, genital corpuscles (a derivative of Pacinian corpuscles only found in genital skin and nipples), Krause end-bulbs, Ruffini corpuscles, and mucocutaneous corpuscles, are important in the erotogenic sensation of fine touch, proprioception, and temperature. It is not possible to have similar erogenic sensations in a phalloplasty with less dense and less specialised nerve endings. [52]

Another consideration is that, under normal conditions, erotic stimulation triggers the release of neurotransmitters to increase blood flow to the penis, causing erection and sensation. [49] The experience and spontaneity of normal erections are not currently possible with phalloplasty, where at best, an inflatable penile prosthesis is required to achieve an erection. While surgeons continue to maximize the potential of phalloplasty, most will agree to replace an organ such as the penis with a skin flap, and prosthesis will have inferior results in all aspects: cosmetic, sexual and urinary function. Patients should, however, be offered phalloplasty first, as the life-long immunosuppression associated with penis transplantation may shorten the life of a recipient.

Immunology and immunotherapy

Even though great strides have been made over the past decade in the understanding of the immunobiology of vascularized composite allografts (VCA), specifically, as it relates to the upper extremity and face transplants, relatively little is known about the specific immunological features of penile transplantation. [53-58] Clinical cases are few, and there are limited experimental data available regarding the immunological characteristics of genital tissue.

Conventional immunosuppressive regimens similar to those successfully used in other types of VCA consisting of poly- or monoclonal antibody induction therapy (anti-thymocyte globulin [ATG], alemtuzumab), followed by triple-drug maintenance immunosuppression with a calcineurin inhibitor (tacrolimus), mycophenolate mofetil (MMF), and steroids have been clinically applied in penile transplantation. [1;4;5] Early reports demonstrate that these protocols sufficiently prevent rejection or immunological graft loss in the first year post-transplant, suggesting a somewhat similar antigenicity of urogenital VCAs as compared to the hand, upper extremity, or face transplants.

Episodes of acute skin rejection were reported in two patients after penile transplantation.[1;4] The rejection could be reversed with either increased systemic immunosuppression, steroid bolus therapy, or topical treatment. This is comparable to the high early skin rejection rates (80-85%) reported for other vascularized composite allotransplants. Chronic rejection remains the leading cause of long-term allograft loss in solid organ transplantation (SOT) and is similarly reported in a series of upper extremities and face transplant recipients. [59-61] It is unknown how such chronic

changes will manifest in penile transplantation until long-term data become available. Normal erectile function is dependent on intact microvasculature. We postulate that new onset erectile dysfunction may be a sign of chronic rejection where microangiopathic changes is a hallmark sign.

Many questions regarding the immunogenicity of penile transplants remain unanswered, specifically how the various individual tissue components comprising the penis will be affected by the pathophysiology of acute or chronic rejection processes. Also, while skin is widely considered to be the most immunogenic component in VCA, possible differences in immunological behavior between the skin component of penile transplants (hairless, highly elastic shaft skin lacking subcuticular fat) and the skin in other types of vascularized composite allografts need to be taken into consideration.

More insight into the underlying immunological mechanism of an alloimmune response after penile transplantation has been gained in some recent experimental studies using new model systems to characterize clinical and histological features of male genital tissue rejection. Sopko et al. have evaluated the effects of rejection and immunosuppression on cavernous tissue using a novel *ex vivo* mixed lymphocyte reaction (MLR) model. [62] The system uses human cavernosal tissue to resemble the donor together with peripheral blood mononuclear cells (PBMCs) to resemble the recipient's immune system in order to evaluate the clinical impact of a controlled alloimmune response (rejection) as well as different immunosuppressive agents on erectile tissue. The group showed that rejection significantly impaired cavernous tissue physiology, decreased smooth muscle relaxation, and was associated with cellular infiltration and apoptosis. Cyclosporin prevented rejection but did not improve tissue relaxation, whereas tacrolimus did not impair corporal smooth muscle relaxation while equally protecting from rejection. This data highlight the importance of optimising immunosuppression specifically tailored for penile transplantation in order to prevent rejection while maximizing corporal tissue physiology as well as functional outcomes.

A robust and easily reproducible murine model to study the unique immunobiology of male genitourinary allotransplantation has recently been established by Fidler et al. [38] Using this model, the group developed a specific 4-grade rejection classification for penile transplantation analogous to the 2007 Banff Criteria for skin-containing allografts. [38;63] Currently, the presence of urethral mucosa and submucosa is not

included in the Banff classification. This study, therefore, represents the first systematic and comprehensive histopathological analysis of allogeneic vascularized composite male genital tissue rejection in a rodent model.

Using human and rat *ex vivo* systems as well as an *in vivo* heterotopic penile transplant model, Lough et al. have shown that specific penile tissue components, including the urothelium, cavernous sinuses (vascular endothelium and smooth muscle) as well as neurovascular structures, all undergo a different rate and pace of rejection. Of note, the group could demonstrate that the cavernosal endothelium and urethral mucosa are one of the first targets to undergo apoptosis during the early phases of an alloimmune response in the setting of penile transplantation. [40] In their *ex vivo* model, the urethral mucosa was the most immunogenic graft component. It led to the highest level of peripheral blood mononuclear cell proliferation in all systems, whereas the neural tissues of the penis remained immune privileged. [64]

Such tissue-specific rejection patterns, in combination with unique anatomical and functional features of a penile transplant, might not only help guide the clinical monitoring of the allograft post-transplant but will also allow for the implementation of new and innovative immune monitoring strategies. For example, the use of urinalysis techniques could allow for the detection of non-invasive biomarker profiles for early rejection monitoring, similar to some of the latest developments in kidney transplantation. [65;66]

In addition to advances in microsurgical techniques, the development of potent and targeted immunosuppressive agents has probably contributed the most to the success story of VCA. However, the use of lifelong, multi-drug, high-dose immunosuppression is associated with significant side effects and toxicities, limiting the widespread application of reconstructive transplantation. Thus, there is a strong effort to develop novel approaches and treatment regimens to favour the risk-benefit-equation and to reduce and minimize or, in an ideal scenario, altogether avoid the need for long-term maintenance immunosuppression by inducing donor antigen-specific immune tolerance, the holy grail of transplantation. [67]

Significant advances in this regard have been made over the past years in clinically relevant large animal studies providing proof of the concept that immune tolerance in

skin-containing VCAs across MHC barriers might indeed become feasible in the near future. [68-70] Also, minimization protocols using donor bone marrow infusion and monotherapy maintenance have been successfully translated into ongoing clinical trials in both upper extremities as well as penile transplantation. [4;71] Redett et al. have used an immunomodulatory regimen for their total penis, scrotum, and abdominal wall transplantation consisting of alemtuzumab and steroid induction, followed by tacrolimus maintenance monotherapy, and an intravenous donor bone marrow infusion which has allowed the burden of conventional triple-drug immunosuppressive therapy to be reduced. Of note, the patient experienced three episodes of slight erythema and rash to the graft. All of these were treated promptly with topical clobetasol +/- topical tacrolimus with rapid and full resolution. At no point did the patient require an increase in systemic tacrolimus levels or the addition of steroid bolus therapy. [4]

As the field of penile transplantation continues to evolve, rigorous experimental data from both preclinical animal models and human studies are needed to elucidate further the molecular mechanisms underlying penile tissue alloimmunity. Ultimately, this data will guide the future development of optimized diagnostic and therapeutic protocols that can prevent rejection and ensure long-term functional restoration.

Clinical differences between penile transplantation and phalloplasty

Phalloplasty is the most convenient, accessible, available, and safest reconstruction option in terms of avoiding toxic immunosuppression. If the result is satisfactory to the aphallic patient, the risks of immunosuppression and the complex prolonged workup can be avoided. However, despite extensive attempts by experienced surgeons, the results are often unacceptable to patients and do not produce an aesthetically comparable organ [72], as it violates one of Gillies' Commandments' of not replacing "like with like" [8]. Rashid et al. describe the current disappointing difference between "the dream and the reality" of phalloplasty.[44]

While the radial forearm free-flap (RFFF) phalloplasty is thought to be the "gold standard" technique for complex penile reconstruction, it is prone to unacceptably high rates of urinary strictures and fistulas as well as prosthesis-associated complications such as extrusion and infection. A recent meta-analysis by Yao et al. evaluated 925 RFFF phalloplasties and reported a 7.4% partial/distal flap loss, 30% urethral fistulas,

and 8.2% urethral strictures. While 40% of the urethral fistulas were able to be managed conservatively, they present significant morbidity for the patients. [72] In one of the largest single-center experiences with RFFF phalloplasty, Monstrey et al. report a 41% incidence of urologic complications and a 44% rate of penile prosthesis removal. [73] Similar complications are reported with the anterolateral thigh flap phalloplasty, with the most common being the formation of urethral fistulas (22%) and stricture/stenosis (7%). [74] Segal et al. report a 56% erosion and infection rate following implantation of the intra-penile prosthesis (IPP). The mechanical failure of the device was rare. [75] Post phalloplasty, there are still significant rates of patients not being able to urinate normally or have sexual intercourse. [76] Additional concerns regarding autologous phalloplasty include the unsightly donor site morbidity that results from tissue harvest or the lack of donor tissue in multi-limb amputees such as severely injured military personnel. [12] These considerations may rule out autologous reconstruction in some patients.

While surgeons continue to maximize the potential of phalloplasty, most will agree to replace an organ such as the penis with a skin flap, and prosthesis will have inferior results in all aspects including cosmetically, sexually, and in terms of urinary function. Nevertheless, patients should be offered phalloplasty first, as life-long immunosuppression may compromise the life expectancy of a recipient.

The surgical procedure of penis transplantation

While the scope of this review does not allow for a step-by-step guide of performing penile transplantation, we include essential points without which a new penile transplant program may fail.

Recipient selection and workup

Careful selection of recipients is paramount to ensure the success of penile transplantation. Patients still able to have sexual intercourse and urinate standing should be excluded. Adult patients that have declined phalloplasty could be considered. Psychological and psychiatric screening is essential. It is critical to exclude mental instability or borderline personality as these may be negatively affected by immunosuppression regimes and may cause non-adherence to medication. [24] Building a relationship with a psychologist pre-operatively is important to ensure the

success of the procedure. The same psychologist should visit the recipient frequently during postoperative recovery in the hospital.

Clinical workup concentrates on general health as well as specific aspects related to penile loss, such as scar tissue and vascular supply around the potential graft bed. In SA and the USA, human immunodeficiency virus (HIV) infection and pulmonary tuberculosis are currently exclusion criteria. Blood tests include blood grouping, viral testing for cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes simplex virus (HSV), BK polyomavirus, Adenovirus, human leukocyte antigen complex (HLA) typing and donor-specific antibodies (DSA) screening. Magnetic resonance angiographic (MRA) imaging was needed in the Boston and Baltimore cases, but not in those done in South Africa where penis loss as a result of complications following ritual circumcision had predictable vascular anatomy. [5;33]

Organ retrieval

Procurement should be from a brain-dead adult donor in a recognised transplant program after obtaining specific consent for penile recovery. As multi-organ donation is likely, coordination with different procurement teams is needed. The team recovering the penis would be in the same physical space as the team recovering solid organs such as the heart, kidneys, or liver. Communication between teams is vital to coordinate the timing of the retrieval of lungs, heart, liver, kidneys, and penis to ensure as short a warm ischemic time for each organ as possible. Dissection of the penile blood supply must be as proximal as possible; the dorsal neurovascular bundle should be dissected to under the pubic symphysis. Before retrieving the solid organs, the following should be in place: 1. Proximal dissection of the dorsal penile neurovascular bundle fully dissected in vascular slings; 2. Proximal dissection of the urethra until the bulbar urethra for penile body transplantation, separated from the corpora and in a vascular sling; and; 3. The corpora cavernosa exposed at the level of the neurovascular bundle ready for transection. In coordination with solid organ removal teams, penile blood vasculature should be transected first without crushing clamps being applied, to prevent prolonged warm ischemia, then the urethra transected second, followed by the corpora cavernosa.

Benches for bench-top surgery for each organ recovered should be prepared with an operating microscope and ice-cold organ preservation solution [such as Custodial-

histidine-tryptophan-ketoglutarate (Custodial-HTK) Brettschneider; Koehler Chemie, Alsbach-Haenlien, Germany] ready for infusion at the penile bench. The retrieval should be tailored to the recipient's defect. For example, in the Baltimore penile transplant, scrotum and abdominal wall sections also had to be recovered. [4] In the Boston case, an extra skin flap to improve blood supply was needed [1], and in the South Africa cases, only the lost penile tissue near flush with the abdomen was replaced. [5;33]

The retrieved penis should be cooled by infusing ice-cold organ preservation solution into the dorsal artery of the penis. Cooling can also be effected by direct injection into the corpora cavernosa avoiding the need to cannulate the small cavernosal arteries. The different vascular structures should be identified as well as the dorsal nerves of the penis dissected free for later anastomosis. Vessels and nerves should be kept long and shortened at the transplant to preserve maximum length, prevent tension on the anastomosis, and maintain a large as possible diameter vessel to ease microsurgery. The spongy tissue of the corpora, when cutting this to the needed length, should be bulging convex outwards to minimize dead space at the anastomosis. The recipient corpora cavernosa act as two large blood vessels supplying the grafted penis. The cavernosal blood vessels should be dissected free and dilated for an attempted anastomosis later with the recipient's cavernosal arteries. The penis should be maintained in organ preservation solution on ice at around 4°C until transplantation. Due to logistical theatre issues, the first South African penis transplant had a cold ischaemic time of about 16 hours, but recovery was normal. [5]

A rotated skin flap phallus, using skin from the inferior part of the laparotomy, should be considered to protect the dignity and prevent the emasculation of the donor. This takes about 30 minutes to create and is worth the effort. [33]

Transplantation of the graft

Depending on the indication for transplantation, the previous penile remnant is exposed. Blood vessels are dissected free, taking care to avoid the recipient's potentially sclerosed dorsal vascular bundle. [41] The deep inferior epigastric, external pudendal, or femoral vessels utilizing a vein graft may be used. The dorsal nerves of the penis should be dissected free for anastomosis with the corresponding nerves in

the graft. Depending on the recipient's pathology, remaining corpora cavernosa and the urethra should be dissected free, and the edges freshened up.

Anastomoses of the erectile bodies and urethra before the delicate microvascular work may stabilize the operating field and ease microsurgery. The deep inferior epigastric arteries or external pudendal arteries should be anastomosed to the dorsal arteries of the penis. Cavernosal arteries inside the corpora should be anastomosed if possible. In the South African cases, cavernosal artery anastomoses were not completed. However, the erectile function still recovered. Corresponding deep inferior epigastric veins or the greater saphenous vein may supply drainage. The operating microscope is set at six to nine times magnification and 9/0 or 10/0 nylon sutures used for the arterial and neural anastomosis. A coupling device may be used for venous anastomosis.

Excess skin should be trimmed as a degree of skin necrosis may occur, but tension should be avoided using interrupted sutures. A drain should be placed to prevent compression on the anastomoses by an expanding hematoma.

Intra-tissue oxygen tension metering, as used in other free flap surgery, is preferable due to the fast and accurate measurements. A Licox™ monitoring system is a good example (Intergra Neurosciences, Plainsboro, N.J. USA). Arterial thrombosis was easily diagnosed and managed in the first South African case due to intra-tissue oxygen tension monitoring. [5]

Outcomes

While the first case from China in 2005 required an early penectomy for "psychological rejection" coupled with skin necrosis [2;77], the next four cases (2014, 2016, 2017, 2018) delivered satisfactory outcomes. [1;3-5] The second case performed in South Africa in 2017 has not been reported in detail yet.[3] However, information on this case is included in Table 1, which summarises clinical outcomes until July 2020.

Table 1. Outcomes and complications of reported penile transplant recipients.

Origin of publication	Cause of penile loss	Operating time (hrs)	Successful surgery	Early complications	Late Complications	Outcomes (patient self-reports)				Graft intact at the time of publication
						Unassisted normal erections achieved	Normal sexual intercourse	Standing urination	Psychological recovery	
China 2005 [2]	Industrial accident	4	No	Infra-red lamp needed to warm up graft. Psychological rejection, skin necrosis, and removal of the graft	NA	NA	NA	NA	NA	No
South Africa 2014 [5]	Ritual circumcision complication	9	Yes	Vascular thrombosis, urethra-cutaneous fistula, minor skin necrosis	Tacrolimus toxicity, transient renal failure, Fungal skin infections. (unpublished data): Significant non-compliance and lost the glans penis, skin, and distal part of his penile shaft. Remain potent and sexually active. He contracted two STIs after rejection controlled that were successfully treated with syndromic medication.	Yes	Yes	Yes	Yes	Yes
USA 2016 [1]	Penile cancer	16	Yes	Rejection seen at the skin; responded to topical treatment	None	Yes	Yes	Yes	Yes	Yes
South Africa 2017 [3] unpublished data	Ritual circumcision complication	9.15	Yes	Minor skin necrosis	(Unpublished data) chronic rejection at around 30 months postoperative treated successfully. The erectile function reduced. Renal impairment Kidney Outcomes Quality Initiative (KDOQI) Grade 3.	Yes	Yes	Yes	Yes	Yes
USA 2018 [4]	Combat-related injury	16	yes	Rejection seen at the skin – responded to topical treatment	None	Yes	Yes	Yes	Yes	Yes

The erectile function was restored or substantially improved in all cases. All transplants reported voiding in the standing position and reported significant improvement in mental well-being. An in-depth qualitative interview assessment of the two South African cases (Chapter 4) reported that penile transplantation should be considered as a lifesaving procedure in a society that severely discriminates against those who failed ritual circumcision. However, despite successful penis transplants, the recipients are still discriminated against in their communities as they failed a rite of passage. Being sexually active and 'normal' again helped them to cope with being ostracised from their communities. Major immunological complications such as hematological cancer, the need for renal replacement therapy, or life-threatening infection have not occurred yet in any of the cases to date. However, the risk remains.

Complications

As reflected in Table 1, early complications related to surgery such as vascular thrombosis, urethral fistula, and infected hematoma were reported. [5] All cases reported so far had less skin necrosis postoperatively than previously expected based on the mapping of vascular territories of the penis [78] and did not need any early skin grafting. [1;4;5] One South African case was reported to have transient renal failure that reversed after a reduction in tacrolimus levels. [5] The other South Africa case remains in mild to moderate renal failure (Chapter 3). Opportunistic infections are likely in this group of patients, an *Alternaria spp.* (a fungal pathogen) was cultured from skin lesions of the first South African case. All cases so far reported various degrees of immunological rejection that responded to treatment, see Table 1. One South African case defaulted on medication and lost about half of his transplanted penis and all skin covering it. He resumed medication, and his skin grafts took, and he remains sexually active without any medical or surgical erectile assistance. The last South Africa case has persistent erectile dysfunction after Banff grade 3 chronic rejection was recently managed.

Future directions

As the field of penile transplantation continues to evolve, rigorous experimental data from both preclinical animal models and human studies are needed to elucidate further the molecular mechanisms underlying penile tissue alloimmunity and to guide the future development of optimized diagnostic and therapeutic protocols that can prevent rejection and ensure long-term functional restoration.

It is likely that the ethical considerations will become more developed, and that acceptance by society will increase as more information about the outcomes and costs of the procedure becomes available. Immunosuppression regimes will likely improve and make the risk-benefit ratio of penile transplantation more acceptable.

Tissue engineering may offer hope for penile replacement in the future. This innovation uses matrices called scaffolds that allow the body's natural cells to grow in and reconstitute an organ. This avoids the risk of immunological complications and avoids the use of donor site tissue. However, except for tissue engineering of the urethra [79], no recent publications have indicated successful penile tissue engineering. [80-82]

The evolution of the technical complexity of transplant surgery is to be expected until complete penile transplantation can be performed. In the first successful case in South Africa, relatively simple vascular anatomy was encountered (Figure 2), while the fourth successful case in the USA significantly increased in complexity (Figure 3).

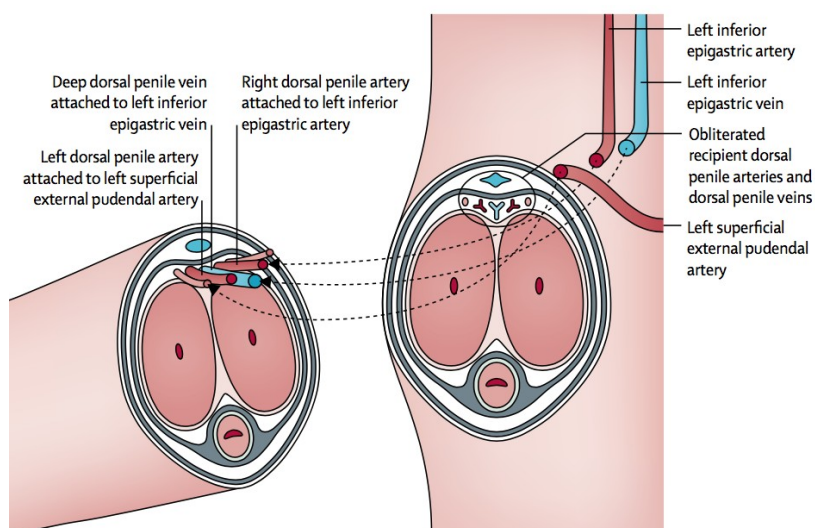


Figure 2. Neurovascular anatomy of the first successful penile transplantation in 2014 in South Africa.

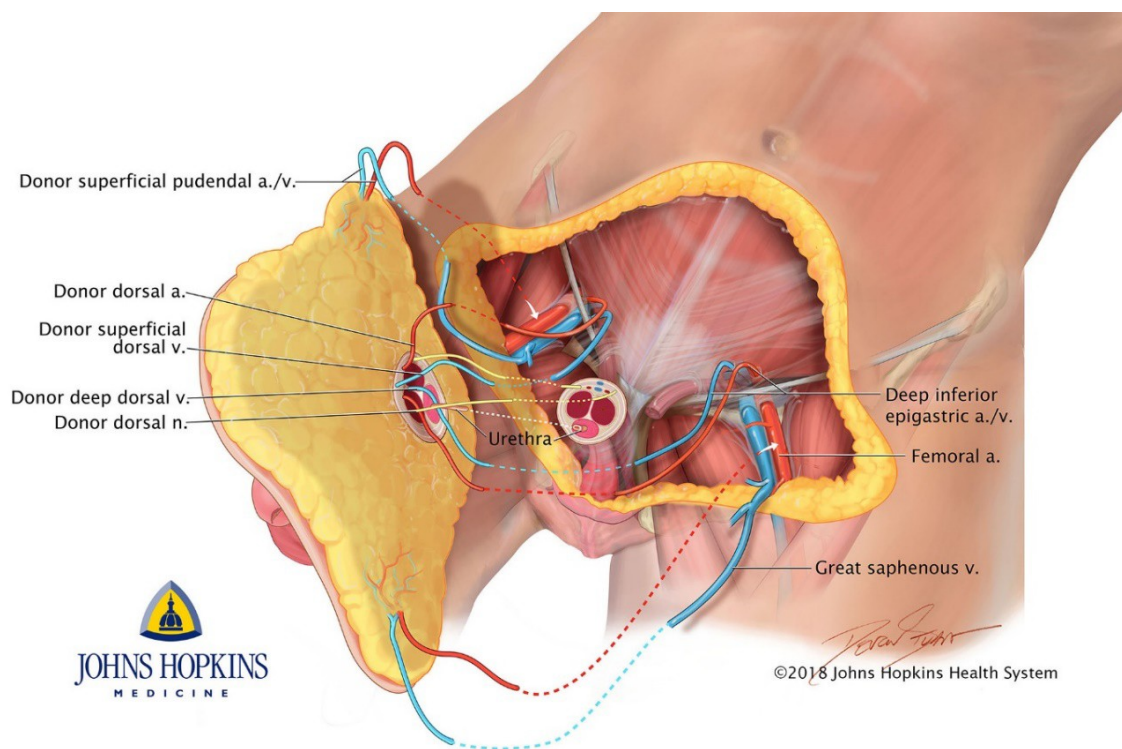
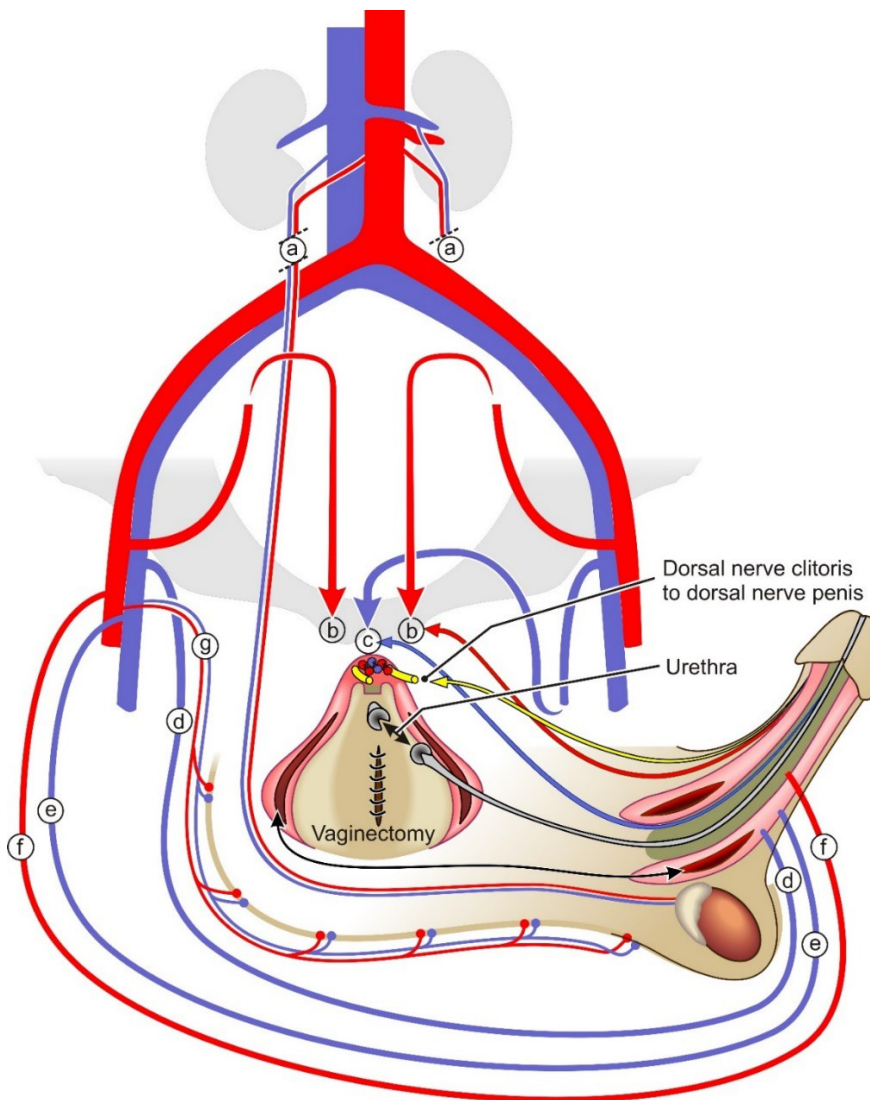


Figure 3. Neurovascular anatomy of the fourth successful penile transplant in 2018 demonstrating evolution in complexity of the surgical procedure.

There is interest from the transgender community in penile transplantation. [83] A group from Gothenburg performed a cadaver en-bloc total penile and scrotum transplantation on a female. [84] They removed the genitalia with attached pubic rami and pelvic blood vessels. They then performed bench dissection to isolate the internal pudendal vessels for anastomosis in the recipient removing bone segments. A drawback of this technique is the severe disfigurement of the donor.

The animal penile transplant study by the group of Siemionow [37] demonstrated that a direct arterial-to-spongiosum technique could have excellent results. Based on this, the group from South Africa performed a cadaveric total genital transplantation, including testes and scrotum (*unpublished data*). However, the authors do not currently support testes transplants in living patients due to the controversy regarding germline transfer. Sterility may be possible with low dose radiation while preserving hormonal function and cosmetic appearance. The ethics related to risks of failure of achieving sterility is complex, needing more careful consideration. The technique suggested, in short, is demonstrated in Figure 4. Donor: laparotomy with transection of gonadal vessels at their origins intra-abdominally, en-bloc scrotoectomy, orchiectomy preserving the gonadal blood vessels. The penile retrieval is similar to the technique of radical

penectomy removing corpora from the pubic rami while identifying the bulbocavernosus artery and proximal neurovascular bundle.



Vascular Anatomy

- (a) Gonadal vessels for anastomosis with testicular vessels
- (b) Deep inferior epigastric arteries for anastomosis with dorsal arteries of the penis
- (c) Left saphenous vein for anastomosis with deep dorsal vein of the penis.
- (d) Right saphenous vein for anastomosis with right corpus cavernosum.
- (e) Femoral artery to corporeal vein graft.
- (f) Femoral artery to spongiosal vein graft.
- (g) Skin blood vessels anastomosed as encountered.

Figure 4. A proposed method for total genital transplantation in female to male gender affirmation surgery.

In the recipient, graft bed preparation is done by vaginectomy, hysterectomy, oophorectomy, exposure of proximal clitoral attachments on pubic rami, and clitoral

glansectomy with identification of dorsal nerve structures. Performing the transplantation is done by a side to side anastomosis of corpora cavernosa of the penis and clitoris, end to end anastomosis of the urethra and direct anastomosis of graft blood vessels on corpora and spongiosum. Deep inferior epigastric vessels are anastomosed to dorsal neurovascular vessels. Lessons from the animal studies above utilising multiple blood supplies should be incorporated.[36;37;85] Therefore two grafts carrying arterial blood from the femoral artery should supply the corpus cavernosum and corpus spongiosum (Figure 4f). Alternatively, the left and right external pudendal artery may be used to supply the corpora cavernosum and corpus spongiosum, respectively. Venous drainage for the corpus cavernosum is created by an anastomosis between the saphenous vein and corpus cavernosum. Testicular vessels are anastomosed to gonadal vessels and skin blood vessels to the scrotum.

Conclusion

Outcomes for penile allotransplantation appear very promising with superior aesthetic and functional outcomes as expected when adhering to the Gillies fundamental principle in plastic and reconstructive surgery of replacing 'like with like.' Workup of recipients and donors, psychological and ethical preparation, surgical execution, postoperative care, and immunotherapy all contribute to the complexity of these procedures. A well-functioning multidisciplinary team is needed for penile transplant success. Modern immunologic advances hold the key to a successful future for penile transplantation. Trans male patients undergoing gender affirmation surgery may benefit in the future from penile transplantation.

Competing interests

None declared

Review criteria

The authors draw from their knowledge to select several original manuscripts of the topic. Also, the following databases were searched in English: Pubmed, Embase, ClinicalTrials.gov, and grey literature using Google and Google Scholar to find relevant newspaper articles. Key search terms included: penile transplant, penis transplantation, penile allotransplantation.

Key points

- Penile transplantation offers the best functional and cosmetic result based on adherence to Gillies Principles.
- Ethical and psychological matters arising are complex and deserve careful consideration.
- Immunosuppression knowledge in VCA has advanced, allowing four successful penile transplantations worldwide with relatively few side effects provided patients adhere to therapy.

Glossary terms

Allotransplantation – transplanting organs or tissue between individuals of the same species.

Baltimore criteria for penile transplantation – guidelines to ethically manage a penile transplant program.

Banff classification – a set of observations to grade immunological rejection in transplants containing skin.

Existential suffering – end of life suffering pre-death that is now known to also exist in those needing facial transplants and likely exists in those in need for penile transplantation as well.

Germline tissue transfer – transfer of germinal tissue of procreation that is deemed unethical in transplantation of genitalia due to the absence of informed consent of the donor.

Gillies principles – several principles amongst other the principle of replacing "like with like" in reconstructive surgery to obtain the best possible functional and cosmetic result.

Immunosuppression – suppressing or modifying the recipient's immune system to prevent rejection of transplanted tissue.

Langer's lines – skin cleavage lines that incisions should not cross as this will increase scar formation.

Phalloplasty – the creation of a penis-like structure from free vascularised skin flaps such as the forearm.

Social death – a condition where the severely ostracised completely withdraw from society.

Solid-organ transplantation (SOT) – organs are consisting of one tissue type, such as the kidney being transplanted and considered to be lifesaving.

Vascular composite allotransplantation (VCA) – transplanting tissues containing a mixture of skin, blood vessels, fat, and muscle.

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Contributions

A van der Merwe wrote the outline of the manuscript and primary contributor to the future directions section

C Cetrulo, R Redett, A Zühlke, T Bivalacqua, A Burnett added content and reviewed the manuscript

G Brandacher was the main contributor to the immunology section, added content to the main manuscript and reviewed the manuscript

MR Moosa added content and reviewed the manuscript.

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CONCLUSION

In the Chapter 'Introduction,' we set out ten parameters we needed to meet to declare the concept of penile transplantation feasible in our setting.

A review of the preceding chapters and addenda of this proof of concept study will show that we have been successful in achieving this aim.

These parameters and how they were satisfied, in italics, were:

1. Our transplant team, experienced in all aspects of renal transplants, should be able to learn and extrapolate from existing knowledge the skills needed to perform penile transplantation, which is a type of vascular composite allotransplantation (VCA). *Chapters 1 and 3: In Chapter 1, we described a cadaver study needed for training. The surgical and immunological successes of Chapters 1 and 3 prove we could learn to perform penile transplants extrapolating from existing knowledge. In Addendum 1 and 2, our technique of penile transplantation is documented in two book chapters published in 2019 and 2020.*
2. Urologists on the team were versed in microsurgery. However, the assistance of plastic surgeons experienced in vascularised free flap surgery would be needed to increase the chances of free flap survival. *The plastic surgical team joined our team, and the free vascularised flaps survived.*
3. We considered ethical matters vital to the success of the project; therefore, a bio-ethicist should join the team to guide the study and build bio-ethical capacity. *A bio-ethicist joined the group adding value to challenging situations such as media contact at the first announcement.*
4. We acknowledged the psychological impact of losing the penis. We had to obtain the services of a hospital psychologist who should join the team. *A male*

hospital psychologist joined the team and built a good relationship with the recipients.

5. Government approval to transplant a new type of tissue – the penis should be obtained. *Government approval was obtained to transport and transplant the new kind of tissue in the Western Cape only.*

6. We estimated that penile transplantation should not be more costly than renal transplantation. We based this on the fact that recipients were healthy individuals, there is no need for renal replacement therapy, the use of generic immunosuppressive medication is cost-effective. Based on this, the hospital had to agree to sponsor the project as a 'clinical event.' *Chapter 1 -our hospital made a detailed cost analysis for penile transplants should this be performed privately at our hospital; this came to R253 000 (USD 18 653). The real cost to our health system would be much less as the doctors and nurses are not paid per procedure but are receiving salaries. The biochemical and psychological follow-up is similar to renal transplantation. Chronic medication is the same as for high-risk renal transplantation.*

7. We had to obtain Human Research Ethics Committee (HREC) approval. *With understandable hesitance, after ordering a cadaver study, community leader interviews, and the main team members appearing before the HREC, we obtained permission to proceed in 2011. Chapter 4 reviews the Ethics of penile transplantation.*

8. The penis transplant should restore urinary function to allow voiding while standing. *It was confirmed in Chapters 1, 3, and 5.*

9. The penis transplant should restore sexual function. *It was confirmed in Chapters 1, 3, and 5.*

10. The penis transplant must restore psychological damage. *It was confirmed in Chapters 1, 3, and 5.*

Chapter 6 reveals that two American teams also performed successful penile transplantations – adding weight to the conclusion that penile transplantation, as a concept, is feasible.

Penile transplantation is the latest type of vascularised composite allotransplantation (VCA). The surgical technique may evolve into more complex surgery for more advanced cases such as total penile or genital transplantation for penile cancer or gender affirmation surgery, as described in Chapter 6.

However, the 'Achilles heel' of penis transplantation in our setting is immunosuppression side effects and adherence to medication (see the updates in Chapter 1 and Chapter 3). As the men receiving a penile transplant are likely young, they are more likely to not adhere to medication schedules. Internationally, adherence to medication improves after the age of 25 [1], for renal transplantation at our hospital, the age where adherence improves is 40 years of age. [2] Due to their younger age and risk to non-adherence, electronic measures to send reminders may be an option such as the "TAKE-IT" study in teenage renal transplant recipients where electronic media were used to send reminders to improve daily adherence via a mobile application. [3] Immediately after the transplantations, both patients were very adherent to medication. However, as the challenges of everyday life transpired, and they got used to having a penis, they failed to take medication as prescribed and even seem to forget how difficult life was without a penis. This is evident in that our second case had two admissions for suicide ideation before transplantation but in Chapter 5, the depth interviews, he had to be prompted before remembering suicide ideation.

Future directions in South Africa

Penile transplantation, once the surgical technique is fully established, should take about 4 hours to perform, it should cost less than a renal transplant as the recipient does not need renal replacement therapy and should lead to a full and rapid recovery of urinary and sexual function. Adherence to medication may be improved by more frequent psychology consultations. Due to the severe discrimination, hostility, social isolation, and ostracism faced by those who failed ritual circumcision, a life-saving view of penile transplantation rather than a life-enhancing view should be adopted. Herrington et al. and Bamstedt et al.[4;5] suggested face and hand transplantation should also be seen as life-saving.

Due to donor shortages and the rigorous screening process needed to select participants, penis transplants are unlikely to become the standard of care for the multitude of men who yearly lose their penis in ritual circumcision. The penile transplant program has been stopped for reasons of cost. However, this dissertation provides evidence of a cost-benefit ratio. Penile reconstruction after complete penile loss now has a new gold standard: penile transplantation!

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ADDENDUM A

This addendum consists of a book chapter in which we discuss technical details to perform penile transplantation. The chapter has been published as follows:

Van der Merwe A, Zarrabi AD ZA. Penile transplantation: The last frontier in penile reconstruction. In Martins FE, Kulkarni SB, Kohler TS, editors. Textbook of Genitourinary reconstruction. Springer, 2020, pp. 795-804.



Check for updates

Penile Transplantation: The Last Frontier in Penile Reconstruction

60

Andre Van der Merwe, Amir D. Zarrabi,
and Alexander Zuhlke

60.1 Introduction

The successful transplantation of a human penis potentially changed the genital reconstructive landscape forever [1–3]. For the first time, aphallic patients have the opportunity to have an absolutely normal penis in respect of appearance and function. Normal penile appearance and function cannot be duplicated with phalloplasty or other reconstructive techniques currently available. The so-called "dream" of phalloplasty might be fulfilled by penile transplantation [4]. The goal of performing penile transplantation is to allow the aphallic male to have normal, spontaneous erections for penetrative sexual intercourse, to urinate in a standing position and once again return to a genital identity and -psychological state equal to that of a man with a normal phallus. It would be unethical to perform penile transplantation on demand for individuals who did not suffer penile loss but are simply seeking a larger phallus.

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60.2 Causes for the Absence of a Penis

Causes of the absence of a penis include penile loss secondary to trauma, circumcision – in particular, ritual circumcision with subsequent infection and gangrene, penectomy for penile carcinoma, industrial accidents, congenital aphallia, gender dysphoria in transgender men, surgical disasters such as penile diathermy injuries and amputation by self-mutilation or assault. Depending on the cause, a unique challenge to transplanting of the penis will likely be posed. For instance, radical penectomy for cancer would necessitate a much more proximal approach to penile transplantation than penile amputation secondary to assault. Should a penis be transplanted in transgender men, an even more proximal approach would likely be needed creating challenges regarding blood supply to the corpora cavernosa.

60.3 Contra-indications to Penile Transplantation: Donor

Only anatomically and functionally normal penes should be transplanted. Sexually transmitted diseases have to be clinically and serologically excluded before penile harvesting. Due to the limited numbers of penile transplants performed to date, the ideal donor age is a matter of opinion,

but late teens to early thirties would seem the ideal age group because penile vascular disease is unlikely to be present.

An intact donor foreskin is not essential for successful penile harvesting and transplantation.

60.4 Contra-indications to Penile Transplantation: Recipient

Not every patient requesting penile transplantation is an appropriate candidate for the procedure. Those with enough remaining penile length to have penetrative intercourse and urination in a standing position possible should not qualify for a penis transplant. Only the most severe micropenis would qualify for surgery. Any condition that might make the adherence to post-operative immunosuppressive regimes difficult would be a contra-indication to further work-up. This includes mental illness, substance abuse and geographical location a long distance from the penile transplant team for follow-up. In our experience patients are willing to move to an area close to the hospital to overcome this obstacle. Active infections of any nature would be a contra-indication. It is not sure whether retroviral status should be a contra-indication per se for medical or ethical reasons: It would be disastrous if an HIV positive recipient infects a partner via a transplanted penis. The risk can be managed by keeping the viral load very low, but there will remain a risk, in particular, if anti-retroviral medication is interrupted for a period.

60.5 Ethical Matters Arising from Penile Transplantation

There has been a "revolution" in organ transplantation with the increasing number of vascularized composite tissue transplantations (VCA) such as hand, forearm and face being performed across the globe [5]. These transplantations are in contrast to solid organ transplantation such as liver, heart or kidney where the recipient would demise if the transplantation is not performed, even though the patient may die because of the surgery. In VCA, the patient's physiological life is

not at obvious risk. Ironically, toxicity secondary to immunosuppression may cause solid organ failure or death from solid organ failure, infections or cancer in the recipient.

Patients in need of penile transplantation are usually young. This means they have a large quantity of own life that they might be wanting to trade in part for receiving the quality of life made possible by a normal functioning and appearing penis. The ethical question is whether doctors have the right to impose these risks on recipients, also, do doctors have the right to refuse transplantation in all those who qualify based on the assumption that the patient will be at harm from immunosuppression and does not have the right to decide to accept own risks or not. Choices like these are quite common in urology, for instance, a patient with advanced bladder, or prostate cancer might decide to avoid life-prolonging chemotherapy as the side effects might reduce the quality of life of the time left on earth.

Despite risks of failed surgery and toxic immunosuppression, patients are still very enthusiastic about penile transplantation. Immunosuppressive regimes are nowadays focused on minimal toxicity and often attempt to induce graft tolerance. Bone marrow transplantation from the same donor has reduced immunosuppressive needs in many VCA:s. This might induce a state of total or near total graft tolerance by creating chimerism [6, 7]. It would be paternalistic (ethically wrong) to enforce that all qualifying patients cannot be allowed to consider penile transplantation as an option. Patient autonomy, if applied correctly, should allow patients to decide on the trade-off between quantity and quality of life at current levels of immunosuppression toxicity [8]. Informed consent might be difficult due to potential patient selective hearing when risks are explained. However, as transplant workup is a prolonged process and often takes a year or more, there are multiple contact sessions with the opportunity for risks to become clear to the recipient. It should be made clear at all times that the candidate may withdraw from the transplant program in favour of phalloplasty. The importance of maximum effort to obtain full informed consent cannot be overemphasised.

60.6 Harvesting and Preparing the Penis for Allotransplantation

Penile harvesting forms part of multi-organ procurement which often includes solid organs, skin and corneas. Consent to harvest the penis has to be specifically obtained from the grieving family. One cannot expect a family who consented to "all organs" to be content with penile harvesting. To protect the donor's dignity, the surgical team should offer to create a phallus for the donor by transposing a skin flap from the abdomen down and tubularize it with skin staplers. This takes less than 30 minutes as vascularity of the flap is not necessary. A side table is prepared with ice swabs, ice cold transplant perfusion solution and small vascular cannulas. Fine vascular- and microsurgical instruments must be available. If possible at all, bone marrow should be drawn from the donor for transplantation into the recipient by a haematologist.

When multi-organ harvesting is performed, the surgical team procuring the penis can start simultaneously to the team harvesting the solid organs. The donor will be in the supine position – in addition, for penile harvesting, the lower limbs should be placed in the frog-leg position. Lithotomy is preferred in an obese donor or when proximal corpora are likely to be required for transplantation. A skin incision with a 1-2 cm rim around the penis, similar to radical penectomy, is created. Recipient pathology would dictate the proximal extent of the corporeal transection. In cases of penile cancer where corpora have been in part resected from the pubic bones, one might have to dissect the cavernosal arteries back to the pudenda! artery and create a similar dissection in the recipient. However, the maximal length of the dorsal neurovascular bundle should be preserved by meticulous dissection from under the pubic arch. The dorsal arteries of the penis should be identified during the dissection for easier identification and cannulation later on the bench. An important consideration is the fact that dorsal arteries become much wider proximally. A longer vascular pedicle of the donor penis would also decrease

the needed length of the recipient vascular supply (deep inferior epigastric vessels) therefore saving time during the abdominal dissection. The urethra is dissected to the proximal bulb. The dorsal neurovascular bundle is cleanly transected with a scalpel. Proximal corpora and urethra are transected. Bleeding in the donor is controlled by compression until cardiac arrest in the brain-dead donor is established [9].

On the side table, the dorsal arteries of the penis are cannulated and transplant solution flushed through using gravity. Backflow of the infused fluid via the corporeal bodies would indicate a connection between the dorsal vessels and corpora and may have potential benefit for erectile function. If the calibre of the cavernosal arteries is too small to be cannulated, transplant solution should be flushed directly into the corpora using a syringe and needle, similar to the access used for priapism. The penis should be flushed until clear fluid is seen from the corporeal bodies and skin. Using a microscope at adequate magnification, the neurovascular bundle is dissected to identify the arteries, veins and nerves. These structures should be separated for 3-4 cm to allow easier manipulation during anastomoses. The corpora and urethra are trimmed to the expected transplant length needed as dictated by the pathology addressed. The urethra should be about 2 cm longer than the corpora cavernosa to allow for a spatulated anastomosis to the recipient urethra.

60.7 Preparing the Recipient for Graft Attachment

The patient is anaesthetised in the supine position under general anaesthesia with intra-arterial blood pressure monitoring and suprapubic catheter drainage of urine. Maintaining adequate perfusion pressure during and after the transplantation is critical. The local dissection of the genital area will be guided by the recipient's pathology. A skin incision, circumferentially, to match the calibre of the graft is created. All sizeable blood vessels found in the skin should be carefully identified and dissected free for possible skin drainage of the graft later. All scar tissue must be excised. The

remainder corporeal stump is dissected free until a corresponding calibre to the graft is found. The urethra must be freed and the distal end clean and ready for spatulation before the urethral anastomosis. Troublesome bleeding from these, if present, is controlled with vascular slings.

The dorsal penile nerves of the recipient must be identified in the dorsal neurovascular bundle and dissected free to allow for manipulation during coaptation to the dorsal nerves of the graft. The deep inferior epigastric vessels are a good calibre match for the dorsal vessels of the penis. Blood supply to the cavernosal bodies via the dorsal vessels is probably more common than previously investigated [10]. Incisions over the lateral border of rectus muscles are made to dissect the deep inferior vessels for a distance adequate to transpose them under a skin bridge to the donor vessels. The deep inferior epigastric vessels are dissected free from their origin making sure to prevent kinking when the vessels are brought 180° down. A gentle curve is followed that should improve laminar flow in these vessels. The branches of the deep inferior epigastric vessels must be ligated securely. A bleeder under the skin bridge might cause an unnecessary delay later. The dissection of the deep inferior epigastric vessels continues until adequate length and calibre are achieved.

If the venous match is less than perfect, the long saphenous vein could be dissected and brought into the wound for venous drainage. The deep inferior epigastric artery and vein must be separated with enough space to perform the anastomosis on each vessel without pulling on the other. The artery and vein should be marked anteriorly with a marker pen to prevent twisting when transposed under the skin bridge. Once the deep inferior epigastric vessels are controlled at their origin with vascular clamps, transected at the correct length and flushed with a solution for heparin and saline they are ready to be transposed to the attachment site. This is done by freeing the subcutaneous tissue under the skin bridge and placing a large latex corrugated drain under the bridge. The vessels are then brought into the wound by pulling on the drain, not the vessels. The recipient site is ready when the deep inferior epigastric vessels are in the wound, the corpora and urethra prepared, the dorsal nerves

of the recipient penis identified and bleeding is under control.

60.8 Attaching the Penile Transplant to the Recipient

The cavernosal arteries anastomoses are attempted with 9/0 or 10/0 nylon suture and adequate microscope magnification. It is unsure if the cavernosal anastomosis has a beneficial effect as recanalisation is likely to happen; the time saved not doing it is valuable in an operation that can take 9-16 hours to perform. In the two penile transplantations performed by Stellenbosch University doctors, only one artery was anastomosed. The degree of difficulty of the cavernosal anastomoses should not be underestimated [9].

The dorsal arteries are anastomosed with 9/0 interrupted nylon sutures under microscope magnification. The veins are anastomosed with a coupling device to save time. Clamps on the inferior epigastric vessels are released, and then the arteries are observed for pulsation until their entry into the dorsal neurovascular complex. A Doppler examination to confirm flow will be helpful at this stage as an occluded arterial anastomosis can still transmit a pulse due to a water hammer effect on the thrombus. Backflow of blood via the corpora cavernosa, corpus spongiosum and skin, should be prominent and confirms patency of the arterial anastomosis. The remainder of the corpora cavernosa are closed with 2/0 polyglycolic continuous suture in a watertight fashion. The dorsal nerves of the penis are coapted with 9/0 or 10/0 nylon sutures. The urethra ends are spatulated and a double layer continuous mucosa! anastomosis with 4/0 polyglycolic acid is done followed by the outer layers of the spongiosum with the same suture. The corpora cavernosa and spongiosum should be closed watertight allowing for early postoperative erections. Skin blood vessels observed should be anastomosed if proximity allows. Re-routing and tunnelling of the great saphenous vein to enhance venous skin drainage would be time-consuming and is unlikely to have a major benefit. Intra glans tissue oxygen perfusion monitoring is helpful in the immediate postoperative period. The penis is loosely dressed, to

allow for post-operative erections, with a non-sticky silicone dressing and stabilized with a foam sponge tubed over it and stapled to the skin. The penis should be at about 90° to the body. The glans penis should remain visible to check capillary refill and colour. Movement of the penis should be restricted. A cradle is placed under the sheets of the patient making sure no external pressure exerted on the transplant. Heparin anticoagulation is started intra-operatively.

60.9 Post-operative Monitoring

The patient should be in intensive care or a high care isolation ward. It is critical maintaining the blood pressure at around a mean arterial pressure of 100 mmHg to prevent thrombosis and maintain blood flow to the graft. Tissue oxygen partial pressure is monitored; a sudden drop indicates the need for an emergency return to theatre to revise the anastomoses. The transplant is inspected on day three. Possible skin necrosis at the base is monitored, but only debrided from about a week postoperatively to allow for demarcation. In the Stellenbosch cases, there was about a centimetre and a half of the base debrided in the first case and only very minimal debridement in the second case. Swelling of the skin due to lymphatic obstruction should be expected and poses a high risk for infection (Fig. 60.1). Swelling subsides in a few weeks to months. (Figs. 60.2 and 60.3).

A daily dose of oral phosphodiesterase-5 inhibitor is started on day one postoperatively to ensure erections as early post-operatively as possible.

Access to the patient must be limited to two or three team members who also exclusively do the daily dressings (starting after day three), making sure of absolute sterility. The patient should stay in the hospital for more or less 4 weeks, though this lengthy monitoring as part of the research setting is probably overtreatment. A psychologist, preferably the same one as during workup, should visit the patient daily. The tissue perfusion monitor is removed after 4 days and the suprapubic catheter at 6 weeks once a urethrogram confirmed patency with no leaks at the urethral anastomosis.



Fig. 60.1 Swelling of a penile transplant on the thirty-second post-operative day still visible



Fig. 60.2 A penile transplant at 18 months postoperatively

60.10 Immunosuppression

A detailed report is out of the scope of this chapter. Immunotherapy side effects are the price recipients have to pay to receive a perfect penis. These side effects can be fatal. Common side effects include renal failure, infections such as tuberculosis and fungi, malignancies including

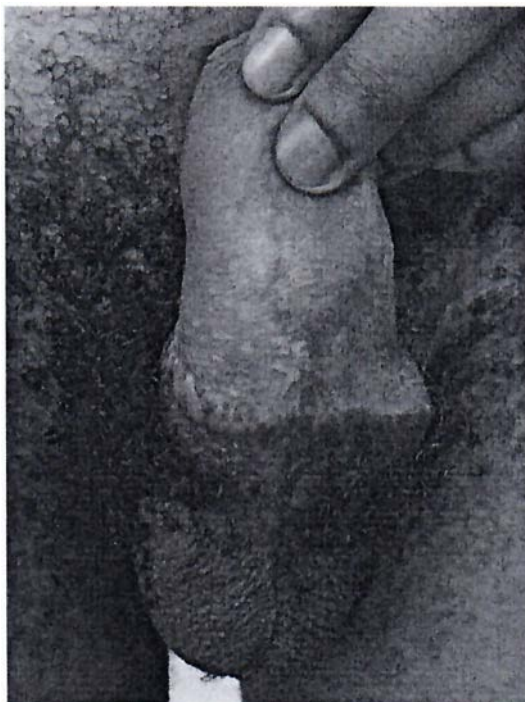


Fig. 60.3 The line of demarcation between recipient and transplant is more visible in the ventral side

haematological cancers and skin changes including abnormal hair growth and pimple like lesions from steroids. The most common reason for non-adherence to the immunosuppression protocol is an objection to skin changes, in particular in younger recipients of solid organ transplants. Patients under the age of 25 are at the highest risk of non-adherence to immunosuppression regimes [11, 12]. Reducing immunosuppression toxicity is of paramount importance. If this can be achieved by concomitant same donor bone marrow transfusion, it will be a major step forward in the long-term health of the recipient. Drug requirements could be significantly reduced as a degree of graft tolerance may be achieved using simultaneous bone marrow transplantation. Close monitoring of blood levels to prevent toxicity is vital. Standard induction regimes could be adapted to local needs by the attending transplant immunologist. Routine- or sentinel biopsies are potentially dangerous and might not yield the information needed in respect of early rejection.

60.11 Conclusion

Penile transplantation has come to stay. While donor shortages will likely impede the frequency of transplantation, a new gold standard in genital reconstruction has been set. Toxic immunosuppression is a barrier to penile transplantation. However, toxicity can be reduced by administering modern regimes including concomitant bone marrow transfusion. At current levels of immunosuppression toxicity, qualifying patients have the right of autonomy to accept these risks if their penis defect cannot be reconstructed or if the penis is absent.

Key Summary Points

- Penile transplantation is feasible, but one of the more challenging genito-urinary reconstructive surgeries due to the protracted work-up and challenging harvesting as well as transplantation surgery.
- The need for penile transplantation may be increased due to war related injuries.
- The young braindead donor needs to have a normal penis and be free of infectious diseases and cancers.
- Immunosuppression might cause solid organ failure and malignancies in the recipient.
- Despite the risks of immunosuppression and failed surgery patients are very enthusiastic about penile transplantation.
- Ethical considerations evolve around "first do no harm" and patient autonomy. Informed consent is essential.
- Harvesting the penis should be done with great care to preserve the essential structures needed to anastomose to the recipient stump.
- The penis should be cooled to about 4 °C prior to storing in an appropriate transplant solution on ice while the recipient is prepared.

- Creating a good blood supply is essential to survival of the transplant.
- Post-operative monitoring tissue oxygenation and blood pressure monitoring is essential. Fluctuations in blood pressure should be avoided as this risks thrombosis of the vascular supply of the graft.
- A transurethral catheter should be avoided. Place a supra-pubic catheter.
- Adhering to the immunosuppression regime is essential for penile graft survival.

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ADDENDUM B

This addendum consists of a book chapter in which we discuss penile transplantation in the context of penile cancer. The world's second penile transplantation performed in Boston, USA, was done after a patient lost his penis from penile carcinoma. The chapter has been published as follows:

Van der Merwe A. The role of penile transplantation after penis cancer surgery. In Martins F, Djordjevic M, editors. Penile Cancer - Challenges and Controversies. Nova Medicine and Health, 2020, pp. 209-219.

Chapter

THE ROLE OF PENILE TRANSPLANTATION AFTER PENILE CANCER SURGERY

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ABSTRACT

Penile transplantation would only be safe in penile cancer cases in long term remission. The risk of early metastases or local recurrence under the influence of immunosuppression is significant. Recurrence of penile cancer is grade and stage dependent.

Considering this during surveillance, patients could be considered for penile transplantation from around four to five years of remission. Informed consent is vital and should include all the toxic side effects of immunosuppression and the stringent follow-up schedule.

The consequences of non-adherence should be clear. A psychological evaluation should be done by a psychologist and social worker experienced in dealing with transplant patients.

Batteries of blood tests are performed over time which gives each time a good opportunity to remind about the risks and informed consent. The ideal case for penile transplantation would be a total penectomy or proximal sub-total penectomy as a radical penectomy may be too difficult, and a partial penectomy does not justify the risks of joining a penile transplant program. Return of erectile function can be expected. The psychological integration of the new penis does not seem to be problematic in the few cases done so far worldwide.

Penile transplantation is an option for qualifying men in long term remission not wanting a phalloplasty after oncological surgery.

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INTRODUCTION

Penile allotransplantation was met with great caution initially, but it appears to be acceptable treatment in the correct circumstances.[1, 2] Penile transplantation creates hope for normal sexual function, urinary function and appearance after the devastating loss accompanied by total-, sub-total- or radical penectomy. Current reconstructive methods do not create a phallus with similar appearance and function. [3, 4] The psychological impact after the loss of a penis is devastating to the patient as well as his partner. In penile cancer, the patient already received the diagnosis of a dreaded disease. While trying to come to terms with this, he loses his penis with an impact on body image and sexual function.

In patients with early penile cancer sexual function would still be possible and a sudden loss of sexual function would have a major impact on the patient and his partner. Immunosuppression in previous penile cancer patients could risk recurrence due to the compromised immune system. Therefore, an extended time of remission would be mandatory before considering penile transplantation as a substitute for traditional phalloplasty. Anatomical challenges will be significant in particular radical penectomy where the corpora cavernosa is removed from the pubic bone.

IS PENILE TRANSPLANTATION POSSIBLE AFTER PENILE CANCER?

The first United States of America (USA) penile transplantation was done in Boston in 2016 [5]. This was worldwide the second successful penile transplantation after the first successful transplantation in South Africa in 2014 [6]. The patient was a 64-year-old male who had a sub-total penectomy and left inguinal groin dissection four years earlier. He was in total remission since penectomy. After penile transplantation he declares marked improvement in body image; he has improving erectile function and sensation is progressing past the base of the penis [7].

RISK OF RECURRENCE OF PENILE CANCER

More than 90% of local and distant recurrence would have occurred at four years post penectomy [8]. It is therefore imperative to wait at least four years before performing the transplantation. As the skin over the recipient penis stump is removed during penile transplantation, the risk for local recurrence would be even less. At informed consent, the risk of later recurrence should be communicated to potential transplant recipients.

ANATOMICAL CONSIDERATIONS

At harvesting, the penis is removed with the urethra as proximal as possible similar to the technique of radical penectomy. After removal of the penis, it is flushed with ice-cold transplant solution at around 3 degrees Celcius. Flushing is done via the dorsal arteries of the penis, cavernosal arteries if possible, and with direct injection into the corpora cavernosa – much like the approach treating priapism. The fluid draining from the penis should be clear. The penis is cooled to three to four degrees Celcius. Bench work for preparation of the penis for transplantation is commenced immediately after the penis is cooled sufficiently. This bench should be prepared in advance and have an operating microscope, good theatre light, vascular- and microsurgical instruments and seated chairs for the surgeon and two assistants. The bench should be outside of the main theatre in an area where very few staff members will transit. The exposed graft is at risk to be colonised by micro-organisms that will flourish once implanted in the recipient.

1. The corpora cavernosa controls the length of the transplanted penis. It is possible to adjust this length by transecting the corpora more proximal or more distal. The length of corpora should be in balance with the amount of skin needed. The skin should be generous; in every successful transplanted case worldwide, so far, a small area of skin at the base of the penis had to be debrided as it was necrotic. The corpora should only be transected after the dorsal neurovascular bundle had been elevated for about two or three centimetres distal to the transection line. The tunica of the corpora should be transected on its own, and after this, the spongy tissue inside stretched before transected. The transection of this tissue should be conical pointing towards the proximal part of the graft allowing for more erectile tissue to be incorporated and longer length of the cavernosal arteries. Anastomosing cavernosal arteries is extremely difficult due to size and the fact that they retract into the spongiosal tissue making it difficult to find.
2. Corpus spongiosum and urethra should be preserved as long as possible to allow wide spatulation and anastomosis later.
3. Skin retained should be more than what one consider will be needed. Excess skin can be trimmed later. Bloodvessels in the skin should be evaluated and preserved for anastomosis – in particular veins that will enhance venous drainage.
4. Cavernosal arteries should be left as long as possible using the conical dissection technique described above. The arteries should be marked with small clips to make identification easier and prevent retraction.
5. Dorsal nerves of the penis should be identified dorso-laterally and dissected free so that the nerves are about three to four centimetres longer than the proximal corpora. Care should be taken not to damage the dorsal arteries or branches of

those vessels. These branches can have a similar appearance to the dorsal nerves in the bench preparation of the penis.

6. Dorsal veins of the penis can be single or multiple. Each one should be preserved as venous drainage is critically important. These veins should be dissected free from the rest of the neurovascular bundle to make anastomoses easier with draining veins in the recipient.
7. Dorsal arteries of the penis should be dissected free from the neurovascular bundle. They have multiple small branches that should be secured properly to prevent penile haematoma post-operatively. It is pivotal to realise that dorsal vessels increase rapidly in size proximally. They should be harvested as proximal as possible under the pubic bone to make anastomosis with for example the deep inferior epigastric vessels.

The penis is preserved and sealed after preparation during the cold ischaemic time in three plastic bags, the inner one containing 500ml of transplant solution to prevent freezing of the penis.

The elements to consider in the recipient is:

1. Arterial blood supply. An excellent inflow into the graft is needed to prevent vessel thrombosis and supply nourishment to the penis. Inflow should be maximal to allow for normal spontaneous- and nocturnal erections. Normal nocturnal erections are essential in the maintenance of the penis. Potential sources of arterial blood supply to the graft are from the deep inferior epigastric arteries and superficial pudendal arteries. A saphenous vein graft may also be used from the femoral artery to the deep dorsal arteries of the penis if this has been saved by groin lymph node dissections in the cases of positive nodal disease. It is important to avoid the dorsal arteries of the recipient penis as a source of blood supply to the graft as these will be damaged and obliterated after the penectomy similar to the circumcision-related penile cases the South Africa group performed transplantation for.
2. Venous drainage takes place via a number of routes. All need to be maximised to reduce postoperative swelling from venous congestion that will increase infection and skin necrosis. The dorsal veins of the penis drain the glans penis and possibly also skin and corpora cavernosa. In during the two penile transplantations at South Africa, it was observed that flushing transplant solution via the dorsal arteries caused a return of fluid via the dorsal veins, corpora cavernosa and corpus spongiosum. One can conclude that interconnections between different parts of the penis are probably more pronounced than previously believed [9]. Options for drainage is the deep inferior epigastric veins and long saphenous veins, if still present. The dorsal veins to the recipient penis should be avoided as above.

3. Dorsal nerves of the penis should be dissected free from the remaining penile tissue in the recipient. The orgasmic function is via the dorsal nerves. Therefore all efforts should be made to find them using microscope dissection if needed. Planning during the donor harvesting should be such that the donor dorsal nerves are about three to four centimetre longer than the graft as part of the neurovascular bundle. This allows for nerve anastomoses without the need of a nerve graft. A nerve graft in the first USA case that received penile transplantation for penile cancer might have caused the delay in sensation recovery. Anastomosed nerves grow at about 5 mm per week. In the South Africa cases, this growth was about half the normal rate. Retarded nerve ingrowth is presumably caused by immunosuppression. In both South African cases, full sensation returned within eight months of surgery. In penile cancer cases without nerve grafts, the same rate could be expected.
4. Corpora cavernosa should be fixed with a few dissolvable polyglycolic acid sutures ventrally to allow movement free anastomosis of the corporeal arteries.

The surgery would be greatly affected by the recipient genital remainder after penectomy.

In the case of sub-total penectomy, such as the first USA case, anatomy would lend it to surgery similar to penile transplantation after penile loss from ritual circumcision such as the two cases done in South Africa.

PRE-TRANSPLANT INVESTIGATIONS

Investigations have the goal to help select cases, exclude cases where the risks are unacceptably high such as unfavourable psychological profile or anatomy, plan surgery, plan immunosuppression and build a team to work towards successful penile transplantation. Active infections such as tuberculosis and HIV should be excluded. A transplant immunologist manages amongst other blood groups, previous exposure to cytomegalovirus (CMV) and donor-specific antibodies (DSA). In simple cases where there are only a pendulous penis defect, pre-operative angiograms and computed tomography (CT) or magnetic resonance imaging (MRI) scans might be an unnecessary cost.

However, after radical penectomy, it would be very helpful to know the extent of the remaining corpora, if any. Also, to know the presence of bulbar arteries in the recipient who had a radical penectomy before would be critical to establish normal blood flow to the spongiosum, glans and urethra.

PROPOSED APPROACHES AFTER DIFFERENT LEVELS OF PENECTOMY

Subtotal Penectomy

One such case has been successfully performed in the USA. Arterial blood supply was from the femoral vessels with a vein graft to the dorsal arteries of the penis. Venous drainage was to the dorsal recipient vein of the penis — the recipient dorsal arteries were obliterated as expected. Another technique could be to make incisions on the lateral sides of the lower rectus muscle for about 20 centimetres and then using the deep inferior epigastric vessels under a skin bridge to be anastomosed in the skin wound to the dorsal vessels of the penis. The corpora cavernosa is sutured in a watertight fashion with 2/0 polyglycolic acid. The urethras are spatulated wide, and the mucosa sutured separately from the adventitia to allow blood to flow in the spongy tissue for venous drainage as well as erections. A urethral catheter should not be used as this might create movement on the penis that might affect the new vascular supply or create infection at the urethral anastomosis site. An adequate size (F16 – F18) suprapubic catheter should be inserted before the vascular anastomoses are started.

Total Penectomy

A very similar approach to the above may be proposed. Expected differences would include that the recipient penile stump will have to be dissected and mobilised as much as possible. The anastomosis may have to be performed in a more proximal manner that will increase the complexity of the procedure. The recipient urethral stump might be very deep and will have to be mobilised as much as possible to allow for a tension-free and spatulated anastomosis as above.

See Figure 1 of an example of a penile transplantation where the recipient had a defect similar to total penectomy.

Radical Penectomy

After a radical penectomy, the challenges to perform successful penile transplantation will be near insurmountable and has not been attempted yet. Fortunately, momentum to perform penile transplantation in trans men is gaining ground. A very similar approach can be followed after radical penectomy.

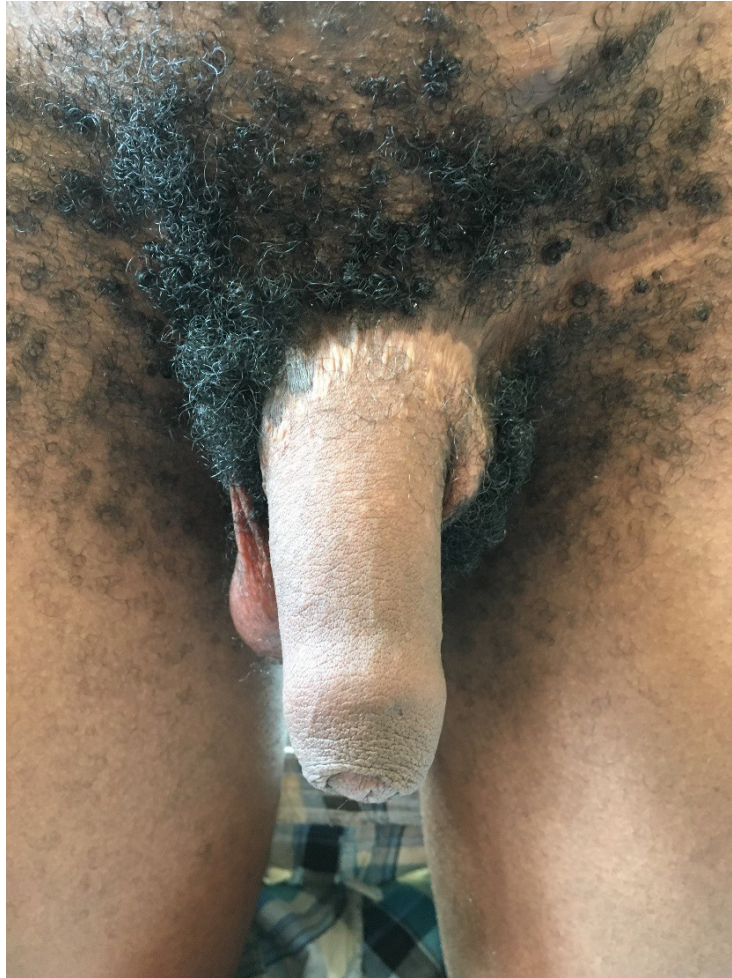


Figure 1. Penile transplantation performed at a similar level of penile defect as a total penectomy. This case suffered from penile gangrene after ritual circumcision.

Principles from a Gothenburg group doing cadaver dissections towards penile transplantation in trans men discovered that the best approach towards securing blood supply to the graft would be by doing a block dissection of blood vessels and nerves from a combined pelvic and perineal approach [10]. This will allow for the bulbo-urethral arteries to be preserved. These arteries play an important role in the perfusion of the corpus spongiosum during erections. The graft's dorsal arteries and veins could with this dissection be more proximally anastomosed. The anastomosis might be in the pelvis increasing the complexity of the surgery. The bulk of donor tissue will be more than any other approach and much time will have to be spent on identifying the different vessels and structures. On-bench, angiograms might be useful. The disfigurement of the donor would also be significantly more than any other approach. This will have to be conveyed in the informed consent process to the grieving family. All efforts should be made to cover

the defect with skin flaps and produce a simple skin flap to resemble a phallus to preserve the dignity of the donor.

IMMUNOSUPPRESSION

While a detailed description is out of the scope of this chapter, it is vitally important that immunosuppression should be as little as possible. The second USA case might have received the perfect regime with a bone marrow infusion of donor bone marrow to induce immunological tolerance. This worked very well as the recipient, a young war veteran, is maintained on a single dose of tacrolimus [5].

ETHICAL CONSIDERATIONS

Patients are at increased risk for cancer recurrence when immunosuppression starts. In addition, the cumulative risk of the side effects on immunosuppression such as renal failure and haematological cancers makes for careful consideration. The recipients are a vulnerable population that would easily engage in an *innovative alliance* where the patient encourages his doctor to do risky surgery as it is perceived as safe enough. *Therapeutic misconception* is very difficult to manage as patients will focus on the perfect outcome where their manhood is recovered. The severe risks and side effects in balance with a good outcome should be repeatedly communicated to patients. As the work-up for these cases is lengthy with psychological evaluations as well as a battery of blood tests at frequent intervals, the opportunity exists to share all information with the patient over an extended period with multiple contact sessions, and he can make an informed decision.

The value of *informed consent* cannot be overestimated. The first case done at South Africa University had a period of non-compliance at around 30 weeks post-operative and lost a large portion of this graft despite returning his immunosuppression levels to high normal and boosting with steroids. Even hyperbaric oxygen for the maximum duration did not save most of the penis. The patient was accepting the complication as he had understood the risks before surgery well and was told on many occasions to be adherent to medication otherwise the graft will reject. As in many young non-adherent recipients of solid organ transplantation, it was the skin rash from the medication that made him stop his medication. As informed consent was in place, a major psychological disaster was avoided. *Patient autonomy* is an ethical principle that allows the patient to decide on his fate.

To prevent a penile transplant program as the risks are perceived too much is *paternalistic* and therefore ethically wrong. In those that qualify for the transplantation informed consent remains the pivotal ethical principal. The cost of penile transplantation should not be more than the cost of renal transplantation. In the case of penile transplantation, no dialysis is needed which negate the cost of vascular access procedures.

CONCLUSION

Penile transplantation is safe if the careful selection of cases is made. After surgery for penile cancer, more difficulties might be encountered than in simple cases such as traumatic loss of the pendulous penis.

KEY SUMMARY POINTS

1. Penile transplantation is feasible and has great improvement in quality of life for the recipient.
2. In penile cancer patients, extra caution should be applied to reduce the risk of inducing recurrence of penile cancer. Recipients must be carefully selected to avoid psychological deterioration after transplantation such as depression (induced by steroid immunosuppression) or psychosis.
3. Anatomical considerations for transplantation will be influenced by the level of penile amputation at curative surgery. This will influence the level of corporeal and urethral harvesting in the donor. The more radical the penectomy in the recipient, the more proximal the donor penis needs to be harvested.
4. Ethical matters revolve around not wanting to harm the recipient, patient autonomy, avoiding well-meant paternalism (to decide for the recipient to avoid surgery due to implied risks) and avoiding an innovative alliance between an eager surgeon and a desperate patient.

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ADDENDUM C

This addendum consists of a response to criticism from within Stellenbosch University that was published in the Journal of Medical Ethics. In this paper, I respond to the allegations in the Journal of Medical Ethics. The response has been published as follows:

Van der Merwe A. In response to an argument against penile transplantation. J Med Ethics 2020; 46:63-64.

In response to an argument against penile transplantation

André Van der Merwe 

Abstract

Moodley and Rennie's paper arguing against penile transplantation stated out of context arguments and wrongly quoted statements. The cost of penile transplantation is much less than portrayed. The burden of cases is much less than is communicated. The men on our penis transplantation programme represent the poorest of the poor and are one of the most discriminated against groups of humans on earth. The false hope said to be created by Moodley is indeed not false hope at all as there is a real possibility that most patients on our waiting list may be transplanted. Moodley argues that government has, in the context of penile transplantation, no duty to cure those who lost a penis after ritual circumcision, but only an obligation to prevent this from happening. A 'yuk' reaction, similarly described in facial transplantation, may be present in colleagues arguing against penile transplantation.

I refer to the paper by Moodley and Rennie published towards the end of 2017.¹ This article was in response to a successful penile allotransplantation performed by a multidisciplinary team lead by me.² Moodley and Rennie correctly state that there was personal communication with me in 2015 regarding the first successful penile transplantation. Personal communication is prone to different interpretation and recollection, and I would like to present what I believe to be more accurate, that is, information about the costs of this intervention.

First, the cost that Moodley and Rennie report requires some context. The price of 243 000 ZAR is the cost our hospital had estimated it would cost for a private patient receiving a penile transplant at a government hospital, including the fees charged for the specialists' services. The real extra cost of this treatment to government is much less; unfortunately, this was not calculated. Cost is the principal basis

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of Moodley and Rennie's arguments. No one on the team received or charged any money. We received our usual salaries which are no extra cost. Theatre costs and ward costs are ongoing and given expenses in an academic hospital, and the money spent regardless of penile transplantation.

In fact, the actual cost of penile transplantation may be compared with renal transplantation. While induction immunosuppression was expensive, it is not more so than some of the high-risk kidney transplants we also perform in this unit. With penile transplantation, one does not need to have potential penile transplant recipients receiving expensive haemodialysis or peritoneal dialysis. Moreover, there is creation of vascular access and peritoneal access for dialysis as is nearly routinely needed for our renal replacement programme. This is a cost not incurred at penile transplantation.

While Moodley and Rennie correctly state that around 250 men lose at least part of the penis per year in South Africa, they do not explain that due to cultural taboos; these men are not allowed to seek Western medical help; therefore, very few will ever enter the waiting lists. At the time of surgery, we had 12 cases on our waiting list. Currently, only three potential cases attend routine workup visits with the rest of them uncontactable, possibly dead by suicide.

During in-depth interviews, I found that the bewildered and depressed aphaallic young men have a particular similar pattern of considering suicide in a strangely uniform way, as the most dignified act to escape their situation. During these interviews, I found that affluent Xhosa people often have ways to protect their young against the brutal complications of ritual circumcision. The men we are helping and giving hope are the poorest of the poor, not allowed to talk about their loss or seek medical help, seen as too weak and failed their culture.

Second, the hope we create for this group of men is judged by Moodley and Rennie to be 'false hope' as they are unlikely to be helped. Indeed, not everyone who lost their penis will be accepted into the programme, and due to donor scarcity, perhaps not everyone will be *transplanted* once accepted into the programme. However, as the number

was small on our waiting list because of the cultural reasons named above, those seeking help have a more than fair chance to receive penile transplantation. By analogy: while an individual playing the National Lottery has virtually no chance of winning the jackpot, their hope is not false because there is a still small chance they might win. Prospects for a young aphaallic man to get a penile transplant once on our waiting list is much bigger than winning the lottery given that the penile transplant programme may continue. In fact, critics of penile transplantation have succeeded to make our local government withdraw any funding such as theatre time, consumables or immunosuppression stating that we need to fund this privately. To obtain financing for someone for an estimated 40 years of immunosuppression is impossible. This effectively closed our programme. In a setting where we also, for example, perform breast reconstruction after mastectomy and bariatric surgery on a routine basis, it is strange that the small numbers of penile transplants anticipated to be performed have to be singled out to save money forwards the fiscal deficit in South Africa.

Third, while penile transplantation should be seen as the gold standard for penile replacement therapy, it cannot be seen as the standard of care. Reconstruction surgery will still help most men with penile injuries. Penile transplantation will only be available for the ones who fully qualify to be admitted to our penile transplantation programme and receive a suitable donor penis.

Fourth, Moodley and Rennie object that high-end and expensive technology is used to perform surgery on indigent third-world patients to the benefit of the first world. But in fact, those of us working for this government service created this option for our poor patients. We only used standard academic hospital equipment and no new purchases were made. The operating microscope we used was not new. We used fine suture material to connect different structures; again, this is standard theatre stock and can hardly be called high tech in an academic hospital. The surgical time of 9 hours will be reduced with more experience.

Moodley and Rennie object that all government efforts related to a penile loss at ritual circumcision should be toward prevention. They claim that to save cost, in the case of treating men who lost their penis from ritual circumcision, the government has no duty to cure at all, but only to prevent, even when the cost is reasonably small and similar or less than that of

Response

a renal transplant. However, they do not consider the implications of this objection to other forms of life-enhancing surgeries, such as the laparoscopic bariatric surgery programme or breast reconstruction after mastectomy, routinely performed at this institution. These would be more costly than one or two penile transplantations per year. The argument that is posed by Moodley and Rennie seems to suggest that the costs of penile transplantation should be allocated to a fund that will effectively reduce the penile amputations in ritual circumcisions in South Africa. It is not clear why they argue that the few penile transplantations performed per year and an effective prevention programme cannot coexist.

As is the case with facial transplantation, much emotion is attached to the transplantation of a penis to a previously aphallic man. This can be a very positive or very negative emotion. Agich and Siemionow comment that public had a 'yuk' reaction to the potential

facial transplant to be performed in the United Kingdom; indeed this backlash was so severe that the Royal College of Surgeons stopped their facial transplant programme temporarily just before the first case could be done.³ In penile transplantation, a similar response might exist. The fact that the transplant relates to genitalia might enhance such 'yuk' responses.

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ADDENDUM D

In this addendum plenary or sub-plenary conference proceedings presented by the student related to the dissertation are listed.

1. Mediterranean Sexology and Andrology Conference, 4 April 2015, Athens - A case of successful penile allotransplantation.
2. International Society on Hand and Composite Tissue allotransplantation Society conference – 15 April 2015, Pennsylvania, PA – electronic live lecture- A case of successful penile allotransplantation.
3. African Society of Sexual Medicine Conference – 28 November 2015, Durban, South Africa – Penis transplantation.
4. SIU 2015: 35th Congress of the Société Internationale d'Urologie (SIU) – 11 October 2015 – The Ins and Outs of Penile transplantation. TED type live and recorded lecture.
5. American Urology Association (AUA) Conference. San Diego, USA. 8 May 2016 – State of the Art lecture: Penile transplantation.
6. Sexual Medicine Society of North America Conference – San Diego, USA 7 May 2020 - Lessons learned from the first successful penis transplant
7. World Conference on EndoUrology – 9 November 2016 - Update on World's 1st Penis Transplant
8. International Society of Vascularized Composite Allotransplantation. Salzburg, Austria, 27 October 2017- What does Survival Mean for a Non-Life Saving Procedure? - from Function, Reproduction and Monitoring - Penis
9. SIU 2017: 37th Congress of the Société Internationale d'Urologie (SIU) – Lisbon, Portugal 18 October 2017 – Genito-reconstructive surgeons pre-conference meeting: State of the Art lecture: Penile transplantation: The world's first successful patient and socio-ethical issues
10. German Urological Association Summerfest. Island Sylt, Germany 1 June 2017 - The World's First and Third successful penis transplantation – why and how?
11. International sexual medicine society (ISSM) Lisbon, Portugal 1 March 2018 – Penile transplantation
12. British Urological Association (BAUS) Annual meeting, Liverpool, 25 June 2018 - Penile Transplantation

13. SIU 2018: 37th Congress of the Société Internationale d'Urologie (SIU) – Seoul, South Korea 6 October 2018. Joint SIU-GURS Symposium: Male Urogenital Trauma – debate against Dr J Zuckerman: Penile transplant vs. Phallic reconstruction.
14. Nord Kongres Urologie, Hamburg, Germany. 15 June 2019. Penile Transplantation
15. Genito-Urinary Reconstructive Society (GURS) meeting Athens. 16 October 2019 - Penile transplantation: Surgical- and Medico-legal issues for a successful procedure
16. SIU 2019: 38th Congress of the Société Internationale d'Urologie (SIU) – 17 October 2019 – GURS session. Penile transplantation.