OPTN Vascularized Composite Allograft Transplantation Committee
Meeting Summary
February 10, 2021
Conference Call

Bohdan Pomahac, MD, Chair
Sandra Amaral, MD, Vice Chair

Introduction

The Vascularized Composite Allograft (VCA) Transplantation Committee met via Citrix GoTo teleconference on 02/10/2021 to discuss the following agenda items:

1. Update – VCA Membership
2. Update – Policy and Bylaws Language Clarification
3. VCA in UNet[SM]

The following is a summary of the Committee's discussions.

1. Update – VCA Membership

UNOS staff presented an update on the implementation of VCA membership requirements.

Summary of discussion:

The application period closed on February 5, 2021. UNOS received VCA transplant program applications from 47 programs out of a potential 66 applications expected. UNOS expects some of the programs who have not yet applied may still submit applications, so UNOS staff will work with those members to try to get their applications processed in time for consideration at the June 2021 OPTN Board of Directors meeting. UNOS staff thanked the members of the VCA Committee that have volunteered to assist the Membership and Professional Standards Committee (MPSC) with the review of the applications.

The Chair asked what the timeline would be for regular review of VCA transplant program applications moving forward, for example, if programs did not meet the deadline for the June Board meeting but still want to submit an application. UNOS staff explained that the programs would be deferred to December for Board approval, but they would still have the option of getting interim approval at the next MPSC meeting. This means there would be a gap in their ability to perform VCA transplants if their application does not go to the Board in June, but that gap could be very small if their application is ready for the June MPSC meeting or a subsequent MPSC meeting for interim approval.

Next steps:

UNOS staff will conduct training for the MPSC on the VCA applications at their meeting later this month, and UNOS staff will provide training to the VCA Committee members who volunteered to review portions of applications.

2. Update – Policy and Bylaws Language Clarification

HRSA staff provided an update from HRSA's meeting with FDA on February 5th, which has implications for the pending VCA policy and bylaws language clarification.

Summary of discussion:

HRSA staff noted that this was an informal response, but that FDA staff provided some practical and useful information. The best approach for addressing questions related to allogeneic implantation, like the questions raised by the VCA Committee regarding certain gland transplants and sentinel flaps, is to contact a specific unit within the FDA called the Tissue Reference Group.[1] The actual clinical providers, the transplanting surgeons, should follow the instructions on their website for requesting this determination. As HRSA staff reviewed informally at the last VCA committee meeting, it appears that sentinel flaps, minced parathyroid gland, and intact parathyroid gland implanted without vascular anastomoses do not meet the regulatory definition or criteria for an organ, just looking at the plain reading of the nine criteria in the Final Rule definition of VCA.[2] HRSA staff anticipate that would be the initial response provided by the Tissue Reference Group.

However, HRSA staff noted that the VCA Committee has expressed interest in possibly obtaining a change in the determination for some of these body parts. It may require a regulatory approach and HRSA's involvement in cooperation with FDA. The Tissue Reference Group would be the first step to go through the FDA to initiate that sort of process, similar to the regulatory change that was made around 2008 to establish extra vessels used in organ transplantation as organs.[3] This might be analogous to the Committee's questions regarding sentinel flaps.

HRSA staff said they would not hazard to comment or speculate on other the body parts discussed, including various types of gland transplants, as asking the Tissue Reference Group would be the best approach. The submission should come directly from the transplant surgeons or the clinicians involved because there are some very specific requirements in the request that the FDA will want to review related to both the clinical and the logistical parameters that are used for the specific body part being transplanted, including cold ischemic time, the types of specific location of where the body part is transplanted, and other issues related to that. The FDA was very open to working with members of the VCA Committee on this.

A member noted that the eight types of VCA transplants include a category for musculoskeletal composite graft segment, and asked why a sentinel flap would not be included in that category. HRSA staff explained that in their reading of the nine criteria defining VCA, free flaps that are vascularized with sutured blood vessel anastomosis and used for either wound coverage or reconstructive purpose would be considered homologous use and would be considered VCA, in contrast to sentinel flaps. The Chair explained the issue was that sentinel flaps are used purely for immune monitoring, although in some cases, they are used for reconstructive function, which is considered homologous use. HRSA staff raised this question with FDA because it creates this dichotomy that if the flap is for immune monitoring only, it would not fulfill all of the criteria that define VCA. One way to address that would be through a regulatory exception similar to extra vessels that are transplanted to reconstruct an organ, but that would have to go through the process described by HRSA staff. The Chair said that surgeons could probably always use fasciocutaneous sentinel flaps for reconstructive purpose to avoid the issue, and suggested that is what will happen if there is not a regulatory change. The Chair thought it would be better to address it in a formal way so that people feel comfortable with the definitions and that it is properly managed. The other consideration is that if the sentinel flap is considered VCA, it would be subject to the same reporting requirements as for a face or hand transplant.

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[1] Tissue Reference Group, FDA, Accessed February 24, 2021, https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/tissue-reference-group.

[2] 42 CFR §121.2

[3] U.S. Department of Health and Human Services, Final Rule, "Organ Procurement and Transplantation Network." Federal Register 72, no. 47 (March 12, 2007): 10922, https://www.govinfo.gov/content/pkg/FR-2007-03-12/pdf/07-1131.pdf.

A member reiterated the concern she raised at previous meetings about differentiating a transplant based on the intention and not on the definition, which is more standardized. The member recommended that any vascularized fasciocutaneous flap should be considered a VCA.

A member agreed with exploring the use of a construct similar to extra vessels for sentinel flaps. HRSA staff said the idea that a myocutaneous flap can serve two functions is fine, such that a flap could be used both for reconstruction as well as an immunologic marker for rejection. However, it puts the surgeon in a situation where if the flap is only used as a sentinel flap for monitoring for rejection, then it leaves the surgeon out on a limb, so to speak. HRSA staff said that is why the FDA is open to considering sentinel flaps, whether or not they are used for reconstruction, to potentially pursue a regulatory change with HRSA to make that an organ category.

A member asked if one approach precludes the other, for example, if the Tissue Reference Group says no, then if members could ask HRSA for a separate designation. HRSA staff said that issue can be addressed if it comes up, but in the interim, HRSA staff have a good working relationship with their FDA colleagues. At this point in time, FDA staff are very open to hearing concerns, and extra vessels provide a precedent in an analogous way since the sentinel flap always will accompany a primary VCA organ.

The Chair asked if it would be possible to schedule a meeting with the Tissue Reference Group. HRSA staff said that in general, the FDA prefers initial contact by email or in writing, but they are open to meeting and subsequent meetings may be face-to-face or via teleconference. HRSA staff said it would be very important to have compelling evidence or arguments, particularly if members are hoping for minced glands to be considered VCA, simply because there may be unintended consequences of setting a precedent for other minced organs. A member asked if the processing component is what complicates these questions for the FDA. HRSA staff said yes, since typically if procedures involve anything more than minimal manipulation, they bring up product safety concerns that are usually not a problem in the solid organ field, even with the longest cold ischemic time of kidneys of 40 to 48 hours. Occasionally, bacteria can creep in with ex vivo perfusion, but in general, once biologic tissue has to be processed and manipulated, it introduces a lot of potential not just for infectious complications but also for logistical and integrity complications.

HRSA staff asked if adrenal gland allotransplants are vascularized or if they are handled more like parathyroid glands in terms of implantation into muscle. A member said he thought that an adrenal transplant was done many years ago but was not sure if it was minced or vascularized.[4] HRSA staff asked the question because there are other glands on the list of covered body parts in addition to parathyroid gland in the head and neck category. A member mentioned that the thymus might be included in a chest wall transplant in the sternum. The Chair agreed but said that would be transplanted as part of the vascularized wall, similar to including prostate as part of a genitourinary organ transplant including penis and urinary bladder, but the prostate gland would probably not be transplanted separately.

Next steps:

VCA Committee members will submit questions to the Tissue Reference Group.

[4] An adrenal gland was transplanted intact in France in conjunction with a kidney transplant: Dubernard et al., "Simultaneous allotransplantation of the adrenal gland and the kidney," *Chirurgie* 121 no. 3 (1996): 181-185, https://pubmed.ncbi.nlm.nih.gov/8945823/.

3. VCA in UNet℠

The Committee discussed updates to implementing VCA in UNet in light of feedback received from HRSA regarding the list of covered body parts[5] since the Committee last discussed VCA in UNet.

Summary of discussion:

One Match Run for VCA

UNOS staff explained that the Committee originally discussed the idea of eight different match runs based on VCA type, but since VCA allocation policy is grouped together in one category, it may better align with policy to have one VCA match run. The candidates would be registered according to the VCA type out of those eight categories, which would align with the membership's transplant program approval. All VCA candidates would show up on the single match run and would be ranked according to policy by waiting time. Organ procurement organizations (OPOs) would have the option to filter based on the VCA they have available to allocate. The Committee did not have concerns with this approach.

UNet Terminology

Previously, the Committee discussed referring to subtypes of VCA in UNet as "anatomic components." UNOS staff recommended using the terminology in the Final Rule, which is "body parts," for consistency to help avoid confusion. The Committee supported this recommendation.

Programming VCA Body Parts in Waitlist

Previously, the Committee discussed having an "other, specify" option in Waitlist under each of the VCA types so that transplant programs could describe the body part needed by the candidate in more detail than provided for by programmed options. This "other, specify" option was based on the "including, but not limited to," language in the list of covered body parts that HRSA staff has since asked the Committee to remove due to concerns about Final Rule compliance. Accordingly, UNOS staff recommend removing the "other, specify" option since it could allow transplant programs to enter body parts that are not covered by OPTN policies and bylaws, even though the list of covered body parts is fairly inclusive. The Committee reviewed the body part options that will be listed under each of the eight VCA types in UNet.

Upper limb

The body part options for upper limb would include right and left. The Chair explained that if he were to register an upper limb candidate, he would select upper limb and then have the option to choose left, right, or click on both, which would mean bilateral. That would include all vascularized body parts from the upper limb that the candidate might need. Even if the candidate just needs a vascularized left elbow, the transplant program would register the candidate for an upper limb and select the "left" option. This means there would not be an option for multiple teams to procure body parts from the same upper limb, for example, if one wants the radial forearm, one wants an elbow, and another wants the shoulder. The Chair said it is probably okay at this point to implement it this way, so if a candidate is registered for a limb, the transplant program will get the limb based on waiting time.

A member said that if somebody can use a hand, somebody can use an elbow, and somebody can use a shoulder from the same donor, it seems silly to preclude that. There should be some mechanism where body parts could be shared, even just by communication across the teams, if the OPTN knows that three teams need different body parts from the same limb and they do not conflict with each other. A member said that VCA is like pancreas in that there is no shortage, so it may not be worth making it

[5] OPTN Vascularized Composite Allograft Transplantation Committee Meeting Summary, December 9, 2020, https://optn.transplant.hrsa.gov/media/4295/20201209_vca_summary.pdf

more complicated at this point. For example, if a program takes part of a limb and then finds out that they need more vessel length, the program would be out of luck. Trying to divide up body parts in more detail seems premature at this point. The Chair agreed that it is premature at this point but said that down the line, the Committee should also think about how to compartmentalize different body parts. A member asked how hard it will be to update these categories later. UNOS staff said this is something the Committee could review as needed and make updates relatively quickly.

Head and neck

The body part options for head and neck would include face including underlying skeleton and muscle, larynx, vascularized parathyroid gland, scalp, thyroid, and trachea.

HRSA staff asked if the language "face including underlying skeleton and muscle" would preclude a face transplant that does not include the skeleton, or if that is not a concern because the procedure would not be performed without bone. The Chair said that even face transplants that primarily used soft tissue grafts included the nasal bone, which is arguably the skeleton. These transplants always include a muscle. A member agreed that there is generally a bony component in a face transplant. The Chair pointed out that the first face transplant performed in France was a partial face transplant that did not include any skeletal component, but did include muscle. The Chair asked if the language as written would exclude recovery of soft tissue without a bone. HRSA staff was not sure that the language would exclude it but felt that the language leaves it possibly ambiguous for someone trying to determine whether or not they have to take some bone just to satisfy the criteria. HRSA staff suggested that there might be another way to word the policy language.

A member suggested wording it as "face including muscle and/or skeletal units." The Chair said that would make sense and asked if it would be acceptable for policy language. UNOS staff said that using "and/or" is generally avoided but offered to work on drafting the language to make it clear that the face transplant may or may not include underlying muscle and skeletal elements. The Chair said that naming "muscle" is probably unnecessary, since it will always be included in the graft, and other components like cartilage and mucosa are not named. The Chair asked what level of detail needs to be included. UNOS staff asked if anything is lost by referring simply to "face" without specifying muscle and skeleton. A member said that the face transplant has to be more than skin to qualify as a VCA so it may not be necessary to name these other components. The Chair agreed.

A member reminded the Committee that this is for allocation purposes, so it is better to keep it simple so OPOs know what they have committed to allocating. The member agreed that "face" alone without the qualifiers would suffice. From an OPO standpoint they will have to explain this to the donor family, so it is best not to get highly technical. A member agreed and said if it is acceptable and appropriate just to use the term "face," he would advocate for that. The Chair said his OPO coordinators always ask exactly how much of the face is needed and what the graft needs to contain, but that may be a separate discussion and it would be simpler not to get into details in UNet. A member said that for OPO purposes, it may be better to just put "face" and perhaps distinguish between "partial" and "whole." The member said the main question that the OPO will have is what part of the face. The Chair agreed the questions are generally whether partial or whole face is needed, and if upper and lower jaw are needed.

A member asked if a vascularized parathyroid gland has ever been transplanted and if it makes sense to include it on the list. The Chair said he was not aware of this type of transplant being performed and suggested that "vascularized" should also be added before "thyroid." The Chair said that these glands were included because if transplanted intact and vascularized, they would be considered VCA, and they may be considered for transplant in the future as organs of the head and neck that qualify as VCA.

The Chair described a trachea transplant performed by a Belgian group that was published in the *New England Journal of Medicine*.[6] The procedure involved implanting the trachea in the recipient's forearm for revascularization and to ween the patient off of immunosuppression, and then transplanting the trachea in the appropriate anatomic location. The Chair asked if there is any regulation in place for a case like this. UNOS staff said that a trachea transplant was performed recently in the U.S. and that is covered by the list of body parts, but the procedure described by the Chair would probably need to go through the Tissue Reference Group for clarification. The Chair thought that recovering a tracheal graft might fall under the FDA's purview with other tissues, but noted that other programs have talked about transplanting vascularized trachea, which would be considered a VCA. A member confirmed that a center in New York performed the trachea transplant mentioned by UNOS staff and that it was vascularized, using a segment of external carotid with superior thyroid artery as the inflow.

A member mentioned that a similar approach was used for larynx at Cleveland Clinic many years ago.[7] The member said that if the trachea needs to be recovered fresh from the OPO, that should be included here under VCA. If the surgical team wants freeze dried trachea, that is tissue covered by the FDA. The Chair said that based on that reasoning, minced parathyroid should be included as well because that also need to be fresh. The member said that it makes since to categorize anything that requires tracking the infectious risk in this area. The Chair agreed but said that is not consistent with the Final Rule definition of VCA. A member said it seems like it should be categorized with cadaveric bone graft, though it would not be processed in the same way, but either way it does not meet the definition of VCA unless there is vascular anastomoses. A member said it will be harder to do these procedures if they fall under the FDA. The Chair said they cannot change the regulatory definition of VCA but suggested there should be a third category, other than organs and tissues, for tissues that have ischemic time but are not reconnected by blood vessels. The Chair said it may be worthwhile to bring this question to the Tissue Reference Group since this seems like a distinct, separate category that does not exist currently.

Abdominal wall

There would be no additional body parts listed under the abdominal wall VCA type. The Chair said this seems reasonable.

Genitourinary organs

The body parts for genitourinary organs would include uterus and penis. UNOS staff noted that transplant programs could use donor acceptance criteria to indicate if other body parts should be included in the graft. A member asked about whether testicle was discussed on a previous meeting. UNOS staff said the Committee previously felt that internal/external male and female genitalia was inclusive enough. The member agreed.

Vascularized glands

The body parts for vascularized glands would include vascularized adrenal and vascularized thymus. The Committee did not recommend any changes.

Lower limb

The body parts for lower limb would include left and right, so the transplant program could specify left, right, or both. The Committee did not recommend any changes.

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[6] Pierre Delaere et al., "Tracheal Allotransplantation after Withdrawal of Immunosuppressive Therapy," *New England Journal of Medicine* 362 (2010): 138-145, https://www.nejm.org/doi/full/10.1056/nejmoa0810653.

[7] Marshall Strome et al., "Laryngeal Transplantation and 40-Month Follow-up," *New England Journal of Medicine* 344 (2001): 1676-1679, https://www.nejm.org/doi/full/10.1056/nejm200105313442204.

Musculoskeletal composite graft segment

The body parts would include latissimus dorsi, spine axis, chest wall, vascularized bone, vascularized muscle, vascularized nerve, and vascularized skin flap.

The Chair did not think that latissimus dorsi needs to be named separately since vascularized muscle would include latissimus dorsi. The Chair asked what someone would choose if they needed a musculocutaneous or osteocutaneous flap, but noted that most of those flaps would come from the upper or lower limb. The Chair asked if the language could reflect some combination of vascularized bone, muscle, nerve, and skin. HRSA staff agreed that the intent is to cover any combination of composite tissue that meets the criteria for VCA, including homologous use and vascularization by anastomoses. The Chair asked if the category could be renamed as "musculocutaneous," but UNOS staff explained that would impact the ongoing membership implementation. HRSA staff said that for OPOs, the most important thing to know is the anatomic location of the body part. UNOS staff suggested having an option for "composite graft of vascularized muscle, bone, nerve, or skin flap," and allowing the transplant program to explain in more detail in the donor acceptance criteria. The Committee supported this approach.

Spleen

There would be no additional body parts listed under the spleen VCA type. The Committee did not recommend any changes.

Next steps:

The Committee will review implementation of the VCA body parts in UNet again at their meeting on 04/12/2021.

Upcoming Meetings

- March 10, 2021
- April 12, 2021

Attendance

- **Committee Members**
  - Bohdan Pomahac, Chair
  - Sandra Amaral, Vice Chair
  - Linda Cendales
  - Lori Ewoldt
  - Bruce Gelb
  - Vijay Gorantla
  - Lawrence Gottlieb
  - Darla Granger
  - Liza Johannesson
  - Nicole Johnson
  - Alexander Maskin
  - Debbi McRann
  - Paige Porrett
  - Debra Priebe
  - Stefan Tullius
  - Mark Wakefield
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
  - Raelene Skerda
- **SRTR Staff**
  - Bryn Thompson
- **UNOS Staff**
  - Kristine Althaus
  - Tamika Qualls
  - Leah Slife
  - Kaitlin Swanner
  - Susan Tlusty
  - Roger Vacovsky
  - Jennifer Wainwright
  - Marta Waris
  - Karen Williams