OPTN Vascularized Composite Allograft Transplantation Committee
Meeting Summary
December 9, 2020
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 12/09/2020 to discuss the following agenda items:

1. Update from OPTN Board Meeting
2. List of Covered Body Parts Policy Language Clarifications
3. Sentinel Flaps

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

1. Update from OPTN Board Meeting

The Chair presented an update from the 12/07/2020 OPTN Board of Directors meeting.

Summary of discussion:

Both proposals sponsored by the VCA Committee, *Programming VCA Allocation in UNet*[1] and *Modify Data Collection on VCA Living Donors*,[2] were approved by the Board as part of the consent agenda.[3] However, the proposal sponsored by the Living Donor Committee (LDC) entitled *Modify Living Donation Policy to Include Living VCA Donors*[4] was removed from the Board agenda due to concerns from HRSA regarding compliance with the OPTN Final Rule.

The Final Rule states, "The OPTN… shall… Identify all covered body parts in any policies specific to vascularized composite allografts."[5] To fulfill this requirement, the OPTN developed a list of covered VCA body parts, which was approved by the OPTN Board in 2016.[6] The LDC proposal refers to this approved, but not yet implemented, list of covered VCA body parts. In reviewing the policy language approved in 2016, HRSA staff raised two concerns:

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[1] Briefing to the OPTN Board of Directors, accessed December 28, 2020, https://optn.transplant.hrsa.gov/media/4211/bp_202012_programming-vca-allocation-in-unet.pdf
[2] Briefing to the OPTN Board of Directors, accessed December 28, 2020, https://optn.transplant.hrsa.gov/media/4215/bp_dec-2020_modify-data-collection-on-vca-living-donors.pdf
[3] Executive Summary, December 7, 2020, OPTN Board of Directors Meeting, accessed December 28, 2020, https://optn.transplant.hrsa.gov/media/4245/board-meeting-executive-summary-20201207.pdf
[4] Briefing to the OPTN Board of Directors, accessed December 28, 2020, https://optn.transplant.hrsa.gov/media/4199/bp_202012_modify-living-donor-policy-to-include-living-vca-donors.pdf
[5] 42 CFR §121.4(e)(3)
[6] "List Covered Body Parts Pertaining to VCA," Policy Notice, OPTN, accessed December 28, 2020, https://optn.transplant.hrsa.gov/media/1879/vca_policynotice_01_201606.pdf

- The list of covered VCA body parts could be interpreted to either narrow or expand the regulatory definition of VCA as established in the OPTN Final Rule. [7]
- While it is acceptable for the LDC proposal to refer to a list of covered VCA body parts located elsewhere in policy, that list must be exclusive. The list of covered VCA body parts approved in 2016 is not adequate for this purpose because it uses the phrase "including, but not limited to."

2. List of Covered Body Parts Policy Language Clarifications

The Chair led the Committee in a discussion of policy language clarifications to address HRSA's concerns as well as questions from members regarding parathyroid transplants.

Summary of discussion:

Policy Language Clarification

The Chair reviewed the nine criteria that define a VCA per the OPTN Final Rule:

Vascularized composite allograft means a body part:

1) *That is vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation;*
2) *Containing multiple tissue types;*
3) *Recovered from a human donor as an anatomical/structural unit;*
4) *Transplanted into a human recipient as an anatomical/structural unit;*
5) *Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement);*
6) *For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor);*
7) *Not combined with another article such as a device;*
8) *Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved; and*
9) *Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient.*

These criteria were derived from characteristics of solid organs to clarify that VCAs are organs rather than tissues regulated by the FDA. The Chair highlighted two of the criteria, noting that the graft must be minimally manipulated and transplanted for homologous use.

The Chair reviewed the list of covered VCA body parts policy language that was approved in 2016:

The following body parts are considered VCAs:

- *Upper limb (including, but not limited to, any group of body parts from the upper limb or radial forearm flap)*
- *Head and neck (including, but not limited to, face including underlying skeleton and muscle, larynx, parathyroid gland, scalp, trachea, or thyroid)*
- *Abdominal wall (including, but not limited to, symphysis pubis or other vascularized skeletal elements of the pelvis)*

[7] 42 CFR §121.2

- *Genitourinary organs (including, but not limited to, uterus, internal/external male and female genitalia, or urinary bladder)*
- *Glands (including, but not limited to, adrenal or thymus)*
- *Lower limb (including, but not limited to, pelvic structures that are attached to the lower limb and transplanted intact, gluteal region, vascularized bone transfers from the lower extremity, anterior lateral thigh flaps, or toe transfers)*
- *Musculoskeletal composite graft segment (including, but not limited to, latissimus dorsi, spine axis, or any other vascularized muscle, bone, nerve, or skin flap)*
- *Spleen*

The Chair presented three proposed changes to address HRSA's concerns: (1) relocate the list of covered body parts in OPTN policy so that it does not appear to either narrow or expand the definition of VCA as established in the Final Rule, (2) modify the list of covered body parts so that the list is exclusive, and (3) update all policies specific to VCA to more clearly identify the body parts covered by those policies. The Committee supported these changes and removal of the "including, but not limited to" language along with the following clarifications, indicated by text that is underlined or struck through:

- Upper limb: any group of vascularized body parts from the upper limb ~~or radial forearm flap~~
- Head and neck: face including underlying skeleton and muscle, larynx, vascularized parathyroid gland, scalp, trachea, or thyroid
- Abdominal wall: abdominal wall, symphysis pubis, or other vascularized skeletal elements of the pelvis
- Genitourinary organs: uterus, internal/external male and female genitalia, or urinary bladder
- Vascularized glands: adrenal or thymus
- Lower limb: any group of vascularized body parts from the lower limb, pelvic structures that are attached to the lower limb and transplanted intact, gluteal region, vascularized bone transfers from the lower extremity, anterior lateral thigh flaps, or toe transfers
- Musculoskeletal composite graft segment: latissimus dorsi, spine axis, or any other vascularized muscle, bone, nerve, or skin flap
- Spleen

Parathyroid Transplants

The Chair explained that the policy clarification is also intended to address questions received by the OPTN as to whether certain parathyroid transplant procedures qualify as VCA transplants. Published journal articles have described a procedure in which parathyroid glands were mechanically minced and transplanted as minced tissue.[8] A similar procedure has been described for adrenal glands[9] and other glands could potentially be treated in a similar fashion. In these procedures, the transplanted tissue does not have its own blood supply and does not appear to meet a number of the criteria that define VCA, including blood flow by surgical connection; minimally manipulated; and perhaps susceptibility to ischemia. The Chair discussed Committee meeting materials from 2015 and 2016 indicating that the

[8] Ayman Agha, Marcus Nils Scherer, Christan Moser, et al. "Living-donor parathyroid allotransplantation for therapy-refactory post-surgical persistent hypoparathyroidism in a nontransplant recipient – three year results: a case report," *BMC Surgery* 16, no. 51 (2016), https://doi.org/10.1186/s12893-016-0165-y

[9] E. Grodstein, M.A. Hardy, and M.J. Goldstein. "A Case of Human Intramuscular Adrenal Gland Transplantation as a Cure for Chronic Adrenal Insufficiency," *American Journal of Transplantation* 10 (2010): 431-433, https://doi.org/10.1111/j.1600-6143.2009.02929.x

Committee was aware that glands would only be considered VCA if they were transplanted with a primary vascularization.

A member asked how islet transplants are regulated. UNOS and HRSA staff explained that allocation of islets is regulated by the OPTN, but the FDA is currently conducting an informal review on whether allograft islet transplants fall within the statutory regulatory oversight and scope authority of the FDA. The FDA regulates the manufacturing of islet cells since this involves extracting the cells from the pancreas, and the cells are considered more than minimally manipulated.

A member asked how parathyroid glands are allocated currently. UNOS staff said that there have not been any allogeneic parathyroid transplants performed in the U.S., though parathyroid transplants have been performed as autotransplants for patients with hyperparathyroidism for years. Accordingly, the technique is well established, but programs are now seeking to apply that technique in an allogeneic context, which has been done in Europe but not in the U.S. A member said it has been done, but it is very infrequent and has only been performed via live donation in patients who are already under immunosuppression.

Members agreed that glands transplanted without primary vascularization are not considered VCA, but asked who would provide oversight for these types of transplants. HRSA staff said that any type of tissue that is not an organ falls under the regulatory oversight of the FDA, including parathyroid allografts that are not vascularized, whether they are minced, fragmented, or transplanted whole without a blood vessel. Accordingly, members agreed that referring to "vascularized" parathyroid gland and "vascularized" glands would be the best way to clarify the policy language, rather than using a term like "non-fragmented" or "intact."

A member noted that by definition, all of the body parts identified in the list of VCA must be vascularized. UNOS staff explained that the intent of the clarification is to make it clear that the list of body parts does not modify anything in the Final Rule in terms of criteria to qualify as a VCA, and make it easy for members to look at the list and see what is considered a VCA and what is not. HRSA staff agreed, explaining that the Committee is not deciding or determining what a VCA body part is; the Committee is making a decision about which body parts VCA policy is going to apply to. If OPTN policy is silent on a particular body part and a surgeon transplants that body part, then the OPTN would not have any enforcement to address that situation. HRSA staff said they were not suggesting any particular approach, but if there is a hypothetical or very rare or unusual circumstance, it is not the end of the world if OPTN policy is silent on that body part at this particular point in time. The Chair said this was an important point and the Committee can feel comfortable with the clarified list of body parts, because there will be room to address any emerging transplants in the future.

A member of the LDC said that their committee faced the same situation when they modified living donor policy a few years ago. At that time, the LDC elected to be silent on the issue of living donor VCA, because VCA had recently been designated as an organ and the LDC did not feel that OPTN policies were robust enough to address the field. It has taken five years for the LDC to circle around to developing policy for living VCA donation. Five years ago, uterus transplants were just beginning to be reported and the LDC had no reason to think it would become what it is today. The LDC member said the VCA Committee can choose to stay silent on a topic but it may be a challenge to get around to updating the policy at a later date. The Chair said that the list is fairly comprehensive of all the VCA transplants that have ever been performed, and VCA transplants that have never been performed but the Committee anticipates that they may be performed in the future.

The LDC member said he thought that the FDA only claimed oversight over tissues that were more than minimally manipulated, and asked whether that would include a parathyroid gland that is removed and

implanted. HRSA staff said it is up to the FDA to determine whether a particular body part has been more than minimally manipulated, but since those glands are not vascularized with suture anastomosis, they would not meet the criteria for VCA.

The Vice Chair asked whether the allocation would occur with an OPTN-approved VCA transplant program even if a procedure did not qualify as VCA, for example, if someone wanted to transplant a portion of a parathyroid that was not vascularized. The Vice Chair sought clarification on how the regulatory distinction between allocation and oversight should be operationalized. HRSA staff explained that allocation is not under any scope of authority by the FDA. For example, the FDA has extensive tissue regulations that have to do with the manufacturing, processing, and procurement of cardiac allograft heart valves, but the FDA does not have any specific allocation-type requirements for the valves. The FDA is silent in that area, but the OPTN is not involved with that either. HRSA staff said they would not envision that there would be any regulatory authority for the OPTN to be involved with the allocation of tissue that is not an organ, and encouraged the Committee not to use islet cells as a model for any other types of body parts or tissues. There are some historical reasons why pancreatic islets became involved with OPTN allocation through pancreas policies. HRSA staff noted that the concern about minimal manipulation is likely preventing islet cells from falling under OPTN oversight but was not sure if this concept could be extrapolated to apply to parathyroid glands.

UNOS staff noted that one transplant program wants to do allogeneic parathyroid transplant as a standalone procedure, not as an add-on to an existing transplant, so there are implications for patient safety and disease transmission. HRSA staff said if that particular program wants to vascularize the parathyroid glands, then they would certainly meet all of the criteria for VCA. However, if they are going to transplant parathyroid glands in some other fashion, whether mincing or fragmenting, then it would not meet the criteria for VCA under the regulation. Members agreed that if a group wants to transplant non-vascularized parathyroid gland into a muscle, then that group does not need to seek approval from the OPTN as a VCA transplant program, and those patients would not be registered or tracked as transplant recipients.

Next steps:

HRSA staff will seek clarification from the FDA regarding regulation of transplants involving minced glands. UNOS staff will review OPTN policies and bylaws for additional clarifications and determine whether the changes will need to be released for public comment.

3. Sentinel Flaps

The Chair presented preliminary feedback from HRSA regarding sentinel flaps.

Summary of discussion:

Preliminary feedback from HRSA indicated that a traditional “free muscular flap” from a deceased donor used for tissue or wound coverage would meet all the criteria of a VCA, since muscle functions include movement and/or tissue cover and protection for internal body structures. A sentinel flap does not serve the same function in the transplant recipient as it does in the original donor, because it is intended solely to monitor for graft rejection, and not to be used as a muscle for movement or protection of internal body structures. Therefore, a sentinel flap would not meet the criteria for homologous use and would not be considered a VCA transplant.

The Chair noted that sentinel flaps have also been used for release of contracture, which would be considered homologous use, and expressed concern that treating sentinel flaps separately from other VCA transplants would create regulatory complexities. The Chair said that the blood flow connection is

the primary distinguishing factor between VCA transplants and other tissue grafts. A member agreed and shared the concern that regulating sentinel flaps separately from VCA transplants would complicate the field. The member said that a sentinel flap will behave the same way as a homologous VCA transplant in terms of being subject to immunological rejection. The member was not sure why considering one criterion would disqualify the entire transplant. The member noted that some people are injecting mesenchymal stem cells into hand transplants before transplanting onto the patient, and that could be deemed more than minimally manipulated. Some programs are also using bone marrow with hand transplants. The member said it is not clear who is monitoring which aspect of the field. If a bone marrow infusion conducted 15 days after a hand transplant causes an infection, it is not clear who to report that to, and how that infection affects hand transplant survival. The field is already complicated and should be simplified moving forward.

A member pointed out that the Committee just discussed how a particular type of transplant that is being performed in the literature does not meet the definition of VCA as defined by the nine criteria. The Committee cannot pick and choose where to take exception to the nine criteria.

HRSA staff offered to approach the FDA, at least informally, to seek possible options that might satisfy the Committee's concerns. Blood vessels that are used with transplanted organs to reconstruct the vasculature may be a useful model. While organs have been transplanted for decades, it was not until around 2008 that HRSA and the FDA issued a regulatory change to consider a blood vessel to be an organ if it was used as an adjunct for reconstruction of vasculature with an organ transplant. This could potentially be a solution for sentinel flaps, since they are used as an adjunct in combination with a primary VCA transplant. HRSA staff were not aware of any musculoskeletal free flaps performed as a primary transplant, and abdominal wall is already specified as being covered by OPTN VCA policies.

A member noted that a vascularized skin or fasciocutaneous flap could either be used as a sentinel flap or for soft tissue coverage. Regardless of the intention, the patient still needs immunosuppression for any vascularized transplant. Additionally, while extra vessels are used to reconstruct the organ, sentinel flaps might be placed at an anatomic location distant from the primary graft, like on a forearm or a thigh to accompany a face transplant. Even if the face graft fails, if the patient still has the sentinel flap, the patient still needs to receive immunosuppression and is at risk, as with any other transplant.

The Chair agreed that skin flaps are different than extra vessels but understood the comments from HRSA staff to mean that the FDA and HRSA might make an exception for sentinel flaps similar to the exception make for blood vessels so that if they are used as part of the same transplant, they are viewed as part of the organ. The member agreed, but expressed concern about accounting for risks, since studies have shown that a face graft might reject while the sentinel flap does not reject. There have been instances of abdominal walls transplanted with intestines where the intestine never rejected but the abdominal wall rejected. Patients receive more immunosuppression than they would have if they had not received the sentinel flap, and there have been lethal complications because of the amount of immunosuppression received. This is a patient safety issue, so the member asked why the Committee would be looking for ways around reporting the sentinel flaps as transplanted organs.

HRSA staff said that it is not a clinical or medical determination, but rather a regulatory determination based on the criterion for homologous use. If the only reason that the sentinel flap is transplanted is to monitor rejection, then from a regulatory perspective, it would not meet the criteria for a VCA. However, the FDA might agree that for instances of the narrow use of a graft as a sentinel flap, it may be

appropriate to include them under the OPTN. The member said that it has not been proven that a sentinel flap actually works as a sentinel, and it is not a standalone diagnosis of the main organ, since teams still end up performing biopsies of the primary graft. The Chair said there is not a lot of literature on this topic, though his paper showed concordance in the higher grades but not necessarily lower grades of rejection.[10] The Chair asked HRSA to discuss the situation with the FDA, and noted that the VCA Committee can still develop reporting structures to request data related to sentinel flaps to address some of the concerns about patient safety.

Next steps:

HRSA staff will seek clarification from the FDA regarding the regulation of sentinel flaps.

Upcoming Meetings

- January 13, 2021
- February 10, 2021

[10] Maximilian Kueckelhaus, Sebastian Fischer, Christine G. Lian, et al. "Utility of Sentinel Flaps in Assessing Facial Allograft Rejection," *Plastic and Reconstructive Surgery* 15, no. 1 (2015): 250-258, https://doi.org/10.1097/PRS.0000000000000797

Attendance

- **Committee Members**
  - Bohdan Pomahac, Chair
  - Sandra Amaral, Vice Chair
  - Linda Cendales
  - Lori Ewoldt
  - Bruce Gelb
  - Robert Goodman, Visiting Board Member
  - Vijay Gorantla
  - Liza Johannesson
  - Nicole Johnson
  - Gary Morgan
  - Paige Porrett
  - Debra Priebe
  - Stefan Tullius
  - Mark Wakefield
- **HRSA Representatives**
  - Jim Bowman
  - Marilyn Levi
- **SRTR Staff**
  - Bryn Thompson
- **UNOS Staff**
  - Kristine Althaus
  - David Klassen
  - Lindsay Larkin
  - Meghan McDermott
  - Elizabeth Miller
  - Liz Robbins Callahan
  - Sharon Shepherd
  - Leah Slife
  - Kaitlin Swanner
  - Susan Tlusty
  - Roger Vacovsky
  - Jennifer Wainwright
  - Marta Waris
  - Karen Williams
- **Other Attendees**
  - Stevan Gonazelz
  - Heather Hunt
  - Randy Schaffer