RM3/RM4 Novel Quantification of Real-Time Lymphatic Clearance: Immediate Lymphatic Reconstruction (L.Y.M.P.H.A) in a Large Animal Model

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Background: The advent of the lymphatic preventative microsurgical healing approach (LY.M.P.H.A), or immediate lymphatic reconstruction, has led to significant decreases in lymphedema after axillary lymph node dissection (ALND). There remains a heightened need to evaluate this microsurgical technique in a large animal model under different experimental conditions using less-invasive techniques. In this study, we report on our experience using venous and skin imaging to assess clearance after lymphadenectomy (LAD) and LAD with LYMPHA using two novel fluorophores in a more clinically translatable model.

Methods: In 10 Yorkshire pigs, a unique fluorophore was injected (ZW-HSA 700 or ZW-HSA-800) into each hind limb. A LAD or LAD with LYMPHA was performed in each experiment. Near-infrared (NIR) molecular imaging was used to evaluate the success of LAD, patency of lymphovenous bypass, and real-time lymphatic clearance. Continuous imaging of the superficial epigastric vein in the torso and adjacent skin was performed throughout the experiment.

Results: Using two novel fluorophores, we were able to quantify lymphatic clearance in both experimental settings (LAD, and LAD with LYMPHA). Vein and skin imaging were successful modalities to assess lymphatic clearance. After lymphadenectomy, mean lymphatic clearance decreased by 66.7% using continuous vein imaging. However, this value decreased by only 33.3% with the addition of LYMPHA. These findings were consistent with results from skin imaging

where lymphatic clearance decreased by 77.1% after LAD and only 28.6% after LAD with LYMPHA.

Conclusion: In this study, we found that skin imaging was a reliable method to detect molecular clearance. We were able to demonstrate the feasibility and success of this clinically translatable modality to evaluate molecular clearance. This model should serve as a springboard for further investigation of the utility of molecular imaging to non-invasively quantify molecular clearance in different surgical scenarios and evaluate its efficacy as a biomarker for lymphatic function.

RM5 **The Effect of Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) on the Development of Upper Extremity Lymphedema Following Axillary Lymph Node Dissection in Breast Cancer Patients**

Henry Ford Hospital, Detroit
Presenter: **Sanjay Rama, M.D.**
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Background:
Post-operative lymphedema is a common complication of breast surgery that has a significant adverse effect on quality of life and carries an increased risk of infectious complications. The Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) involves the creation of a lymphatic to venous bypass at the time of axillary lymph node dissection (ALND) as a means of preventing lymphedema. The goal of our study is to assess the effect of LYMPHA on the development of post-operative lymphedema, need for complete decongestive therapy (CDT), and the incidence of cellulitis.

Methods:
This is a retrospective cohort study of prospectively collected data in breast cancer patients at our institution who underwent axillary lymph node dissection with or without LYMPHA. Descriptive statistics were used to compare post-operative outcomes, which included the development of lymphedema, need for CDT, and occurrence of cellulitis requiring antibiotic therapy. In addition, we compared patient characteristics between those undergoing LYMPHA and those with ALND alone, which included age, BMI, history of smoking, presence of diabetes, along with pre- and post-operative radiation and chemotherapy use.

Results:
In our cohort of 69 patients, 50 arms underwent ALND with LYMPHA, while 20 arms underwent ALND alone. In the total cohort, the mean age was 58.1 years old, mean BMI was 31.3 kg/m^2, 7.1% had pre-op radiation, 57.1% had post-op radiation, 57.1% had neoadjuvant chemotherapy, and 38.6% had adjuvant chemotherapy. In patient arms that underwent ALND with LYMPHA, 18% developed lymphedema compared to 50% of arms that underwent ALND alone ($p=0.007$). In patient arms that underwent ALND with LYMPHA, 18% required CDT compared to 45% of arms that underwent ALND alone ($p=0.02$). In patient arms that underwent ALND with LYMPHA, 0% developed cellulitis compared to 10% of arms that underwent ALND alone ($p=0.02$). When comparing the patient population that underwent LYMPHA to the population that underwent ALND alone, the only patient factor that was significantly different was BMI (mean BMI of LYMPHA group = 30.1, mean BMI of ALND group =34.4, $p=0.04$).

Conclusion:
Our data supports the universal use of LYMPHA at the time of ALND as a means of preventing upper extremity lymphedema and/or cellulitis. Further studies are needed to evaluate quality of life and functional differences between those who had LYMPHA and those who did not.

RM6 **Lymph-Interpositional-Flap Transfer (LIFT): Lymphatic Reconstructive Microsurgery without Supermicrosurgical Lymphatic Anastomosis or Lymph Node**

Transfer

National Center for Global Health and Medicine, Tokyo
Presenter: **Takumi Yamamoto, MD, PhD**
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Background: Long-lasting edema or lymphedema can occur after tissue replantation or transfer due to main lymph vessel damage, but the mechanism is yet to be fully clarified. By identifying factors associated with lymph flow restoration after tissue replantation/transfer, we aimed to develop a new lymphatic reconstructive procedure.

Methods: Medical records of 37 patients who had undergone tissue replantation or free flap transfer and ICG lymphography were reviewed. Clinical findings and postoperative ICG lymphography images were analyzed. Lymph flow restoration (LFR) was evaluated postoperatively using ICG lymphography according to intraoperative findings focusing on lymph axiality; raw-surface in lymph axiality (RLA) and compatible lymph axiality (CLA). Based on the results, a new lymphatic reconstructive microsurgery was developed and applied in clinical cases.

Results: LFR was observed in 65% of the 37 cases. Based on lymph axiality, "RLA (-) and CLA (+)" was completely identical to positive for LFR; 100% accuracy to predict LFR. Based on the concept of lymph axiality, a new lymphatic reconstruction, lymph-interpositional-flap transfer (LIFT), was developed. LIFT could be applied into oncologic, trauma, and established chronic lymphedema surgeries.

Conclusion: Lymph flows can be restored spontaneously after tissue replantation/transfer. The concept of lymph axiality is critical for LFR, and leads to a new lymphatic reconstruction. LIFT allows lymphatic system reconstruction without the need for supermicrosurgery or lymph node transfer.

RM7 **Supermicrosurgical Lymphatico-Lymphatic Anastomosis and Lymphatico-Venular Anastomosis for Intractable Lymphorrhea and Lymphocyst**

Reiko Tsukuura, Tokyo
Presenter: **Reiko Tsukuura, fellow**
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Background

Intractable lympho-rrhea/-cyst (Lr/Lc) can occur after lymph vessel rupture. Since recurrence rate is high after conventional conservative or macroscopic surgical treatments for cases with high lymph output Lr/Lc, secure reconstructive treatment is warranted.

Methods

Thirty-nine patients with Lr/Lc who had been treated conservatively with recurrence of the disease underwent lymphatic supermicrosurgery under indocyanine green (ICG) lymphography navigation. Under ICG lymphography navigation, a major ruptured lymph vessel was identified, and reconstructed with supermicrosurgical procedures; anastomosed to a nearby intact lymph vessel (lymphatico-lymphatic anastomosis: LLA) or to a nearby vein (lymphatico-venular anastomosis: LVA) if available, or just ligated microsurgically. Postoperative Lr/Lc recurrence and lymphedema development were evaluated.

Results

Ruptured lymph vessels could be identified in all cases with the use of ICG lymphography navigation. LLA was performed in 3 cases, and LVA in 35 cases; in 1 case, no recipient vessel was available and the ruptured lymph vessel was just ligated. No cases showed recurrence of Lr/Lc, but lymphedema developed in 1 case where the ruptured lymph vessel was ligated.

Conclusion

ICG lymphography is useful to identify a major ruptured lymph vessel, which is critical for the treatment of intractable Lr/Lc. Lymphatic reconstruction should be performed with either LLA or LVA as possible, because simple ligation may cause postoperative lymphedema.

RM8 **Benefits of Arborized Anastomotic Technique in Immediate Lymphovenous Anastomosis for the Prevention of Breast Cancer Related Lymphedema**

University of South Florida, Tampa
Presenter: **Brielle Weinstein, MD**
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Background

Breast cancer related lymphedema (BRCL) is a chronic, progressive disease that poses tremendous physical, psychosocial, and financial burden on patients. To date, there are multiple non-surgical treatment options available. However, they require lifelong participation, patient compliance is poor, and therapy imparts a substantial negative impact on daily life. Here, we recognize that prevention of lymphedema will likely be the ultimate goal for this population.

Reverse lymphatic mapping (RLM) and immediate lymphovenous anastomosis (ILVA) at the time of axillary lymph node dissection (ALND) is emerging as a new potential therapeutic paradigm to decrease the incidence of BRCL in high-risk patients. ILVA has been demonstrated to impart decreased early lymphedema incidence, however, there is a paucity of literature regarding technique variability.

Methods

59 patients underwent RLM and ILVA at time of mastectomy and ALND. All patients were followed prospectively in multidisciplinary lymphedema clinic (plastic surgery, physical therapy, dietary, and case management) at three-month intervals with clinical exam, circumferential limb girth, and bioimpedance spectroscopy (BIS). Intra-operative technique was selected based on patient specific anatomy after co-dissection with the surgical oncologist. Descriptive statistics and Fisher exact test were utilized.

Results

57 patients met inclusion criteria for analysis. Therapeutic adjuncts included adjuvant radiation 36 (71%), neo-adjuvant chemotherapy 47 (82%), and adjuvant chemotherapy 19 (42%). 19 (33%) patients underwent end-to-end only, 33 (58%) arborized technique only, and 5 (9%) combined. There were no differences in age, BMI, tobacco use, or race between groups. 50 end-to-end anastomoses and 94 lymphatics anastomosed with arborized technique were performed in the cohort. On average, 2.26 ± 1.41 lymphatics were anastomosed per patient in end-to-end and 2.64 ± 0.78 per patient with arborized ($p < 0.30$). Mean operative time for end-to-end only was 4.55 ± 1.39 hours and 3.49 ± 0.62 hours for arborized ($p < 0.005$). Rate of lymphedema despite lymphatic reconstruction for the entire cohort was 7% at a mean follow up of 224 days. In the end-to-end technique this rate was 21% and 0% in the arborized and combined technique ($p < 0.02$).

Conclusion

For patients at high-risk for developing BCRL, advances in RLM paired with patient specific ILVA have put forth promising early evidence of disease prevention as compared to historical controls. This technique data demonstrates that patient specific lymphatic reconstruction with as many lymphatics as possible in an arborized fashion not only confers benefit for success in preventing lymphedema but also decreases operative time.

RM9 **Lymphovenous Anastomoses Are Not Occluded By Compression Therapy. Experimental Model in Pigs.**

Victor Babes University of Medicine and Pharmacy, Timisoara
Presenter: **Alexandru S Nistor, M.D., Ph.D.**
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Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

Background

Post-operative compression therapy after LVA's is still debated, with no documented direct evidence for or against it. We propose an experimental model which allows to measure pressure gradient applied by compression at the level of the anastomosis and assess the immediate post-op and 7 day patency of the LVA following compression therapy.

Methods

After ICG mapping, eight lymphatico-venous anastomosis were performed in 6 female experimental pigs (average 41.2 kg), one in each hind limb of the animal, in lymphatic vessels ranging between 0.3-1.2 mm (average 0.64 mm) in diameter and correspondingly sized veins. Immediately after the anastomosis, perfusion is assessed via distal Patent Blue V subcutaneous injection, ICG mapping and transit-time ultrasound flow measurement (AureFlo, Transonic, USA). After confirming the patency, the left hind limb was bandaged using mild compression and the the right limb using high compression. Pressure after compression was measured and standardized using an intra-compartmental pressure monitor to 40 mm Hg on the right limb and 20 mm Hg on the left limb in three animals and 40 mm Hg on the right limb and no compression of the left limb in the remaining three animals. Compression therapy was maintained with re-tightening of the compressive bandages every 24h for 7 days, followed by bilateral surgical re-exploration of the LVA sites and re-assessing of anastomosis perfusion. Histological examination of the LVA's were performed after surgical explantation.

Results

Post-op, all except one 0.45mm LVA were patent. The occluded LVA was redone. Both Patent Blue V and ICG mapping showed good patency in all other LVA's with no venous reflow. At re-exploration of the LVA sites, occlusion of the anastomosis was noted in 2 LVA's (66%) with no compression, while in all of the limb treated with 40 mm Hg compression, all LVA's (100%) were patent as observed by means of Patent Blue V and ICG. Transit-time ultrasound flow measurement showed a higher flow velocity in the 40 mm Hg compression site compared to the 20 mm Hg site. Histological examination of the occluded LVA's showed thrombus formation with no acute inflammatory response.

Conclusion

Our study provides direct evidence that compression therapy following LVA is useful to maintain LV anastomosis patency, by increasing the intra-compartmental pressure and thus augmenting the lymphatic flow through the anastomosis, preventing venous reflow and late occlusion of the anastomosis.

RM10 **The Discover Study: Intraoperative Real-Time Microscope-Integrated Optical Coherence Tomography-Guided Lymphaticovenular Anastomosis in Peripheral Lymphedema**

Kameda Medical Center, Kamogawa
Presenter: **Akitatsu Hayashi, MD**
Akitatsu Hayashi, MD
Kameda Medical Center, Kamogawa, Japan

Background: Indocyanine green (ICG) florescence imaging and ultrasonographic imaging have been reported to be useful for intraoperative identification of functional lymphatic vessels, which is crucial for successful lymphaticovenular anastomosis (LVA). Recently, optical coherence tomography (OCT), which uses reflection of near-infrared light to generate images, has become a game changer in diagnosis, management, and surveillance of ophthalmic diseases. We present new capabilities of intraoperative real-time microscope-integrated OCT (iOCT) for imaging of the lymphatic vessels during LVA in secondary lymphedema, which may address issues regarding the conventional imaging modalities.

Methods: One hundred-three secondary upper extremity lymphedema (UEL) patients who underwent LVA were classified into two groups, iOCT group (n=48) and non-iOCT group (n=55). In iOCT group, 1) the accuracy of iOCT in detecting the lymphatic vessels was estimated by calculating and comparing the sensitivity and specificity of iOCT with ICG lymphography findings, 2) the correlation between the thickness of the lymphatic vessel wall measured with iOCT and that with histological examination was investigated, and 3) the quality of the anastomosis was assessed using iOCT. Intraoperative findings and postoperative lymphedematous volume reduction were compared between the groups.

Results: One hundred and fifty-three lymphatic vessels were assessed in iOCT group. The sensitivity and specificity of iOCT was 97.4% and 100%, retrospectively. The thickness of the lymphatic vessel wall, which was demonstrated as white region with iOCT, correlated well with the thickness of smooth muscle cell of the lymphatic vessels in histology analysis (correlation coefficient: 0.981). This system showed unprecedented clear image of the anastomotic site after LVA, enabling precise assessment of the quality of the anastomosis. UEL index reduction was significantly greater in iOCT group than that in non-iOCT group (13.3 • }4.9 versus 7.8 • }3.4, *P*=0.037).

Conclusion s: The iOCT provides images with extremely high resolution, allowing precise appraisal of the lymphatic vessel and the quality of anastomosis and effective LVA. This advanced technology has infinite possibilities and may open new frontiers in the field of lymphatic surgery.

RM11 **An Anatomical Study of the Lymph Collecting Vessels and Clinical Applications of Lymphatic Vessels Preserving PAP (LpPAP) Flap Using Pre- and Intra-Operative Indocyanine Green (ICG) Lymphography**

Ryo Karakawa, Tokyo
Presenter: **Ryo Karakawa, MD**
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Background

The profunda femoris artery perforator (PAP) flap is gaining popularity in microsurgical reconstruction. One of the complications that can occur after the PAP flap transfer is donor-site lymphedema. Previous study reported that lymphedema of donor-site leg occurred in 10 % of patients who underwent breast reconstruction using a PAP flap. We hypothesized that PAP flap elevation using pre- and intra-operative indocyanine green (ICG) lymphography will reduce the risk of postoperative donor-site lymphedema. The aim of this study was to evaluate and establish a safer technique for elevation of a lymphatic vessels preserving profunda femoris artery perforator (LpPAP) flap using pre- and intra-operative ICG lymphography. In this presentation, we also evaluate the anatomical relationship between the PAP flap and lymph collecting vessels.

Methods

From July of 2018 to January of 2019, 24 patients with soft tissue defects after tumor resection underwent reconstruction using PAP flaps. The lymph collecting vessels at the medial thigh area were identified using pre- and intra-operative ICG lymphography. A PAP flap was elevated taking care not to damage the lymph collecting vessels (Fig.1). After flap elevation, the length

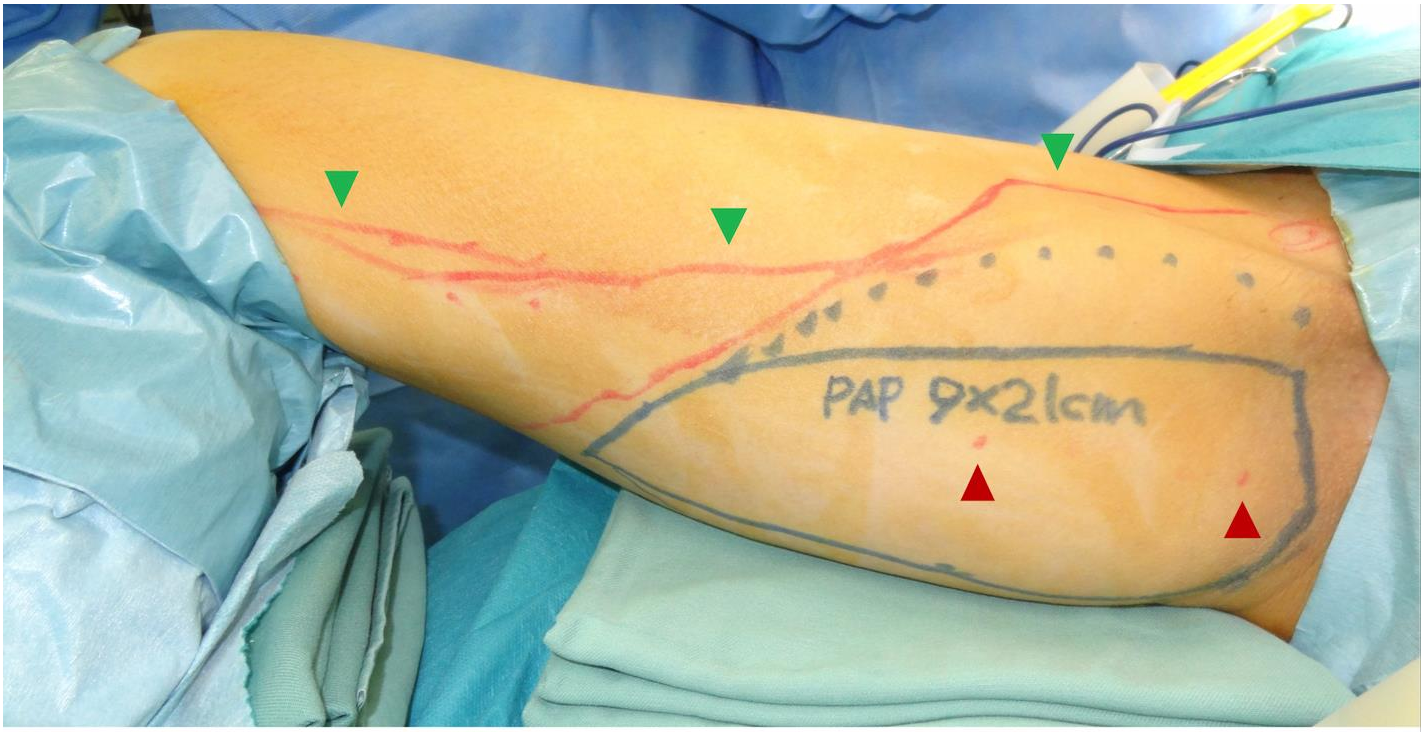
from the medial femoral epicondyle to the intersection of the lymph collecting vessels and the anterior edge of the gracilis muscle was measured.

Results

PAP flaps survived completely in all cases. In all cases, using intra-operative ICG lymphography, surgeons confirmed that the lymph collective vessels in the medial thigh region were left intact. There were no donor site complications such as lymphedema or lymphorrhea. The results were summarized in Table 1. The relationship between the lymph collecting vessels and the anterior edge of the gracilis muscle was shown in Figure 2. The average length from the medial femoral epicondyle to the intersection of the collective lymphatic vessels and the anterior edge of the gracilis muscle was 9.7±1.6 cm.

Conclusion

The elevation technique of a LpPAP flap using pre- and intra-operative ICG lymphography is effective in reducing the risk of damage to the lymph collecting vessels, and thus reducing the chances of postoperative lymphorrhea or iatrogenic lower limb lymphedema.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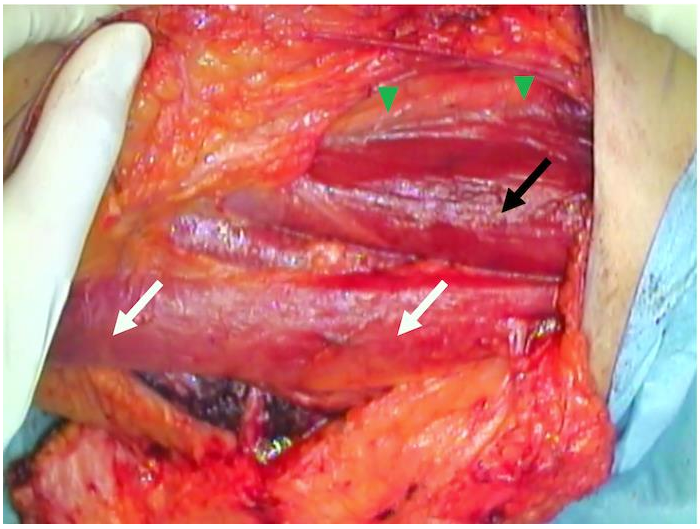


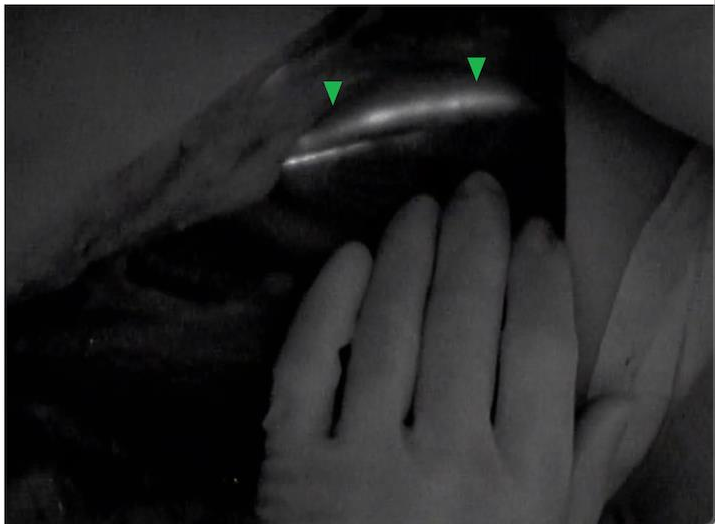
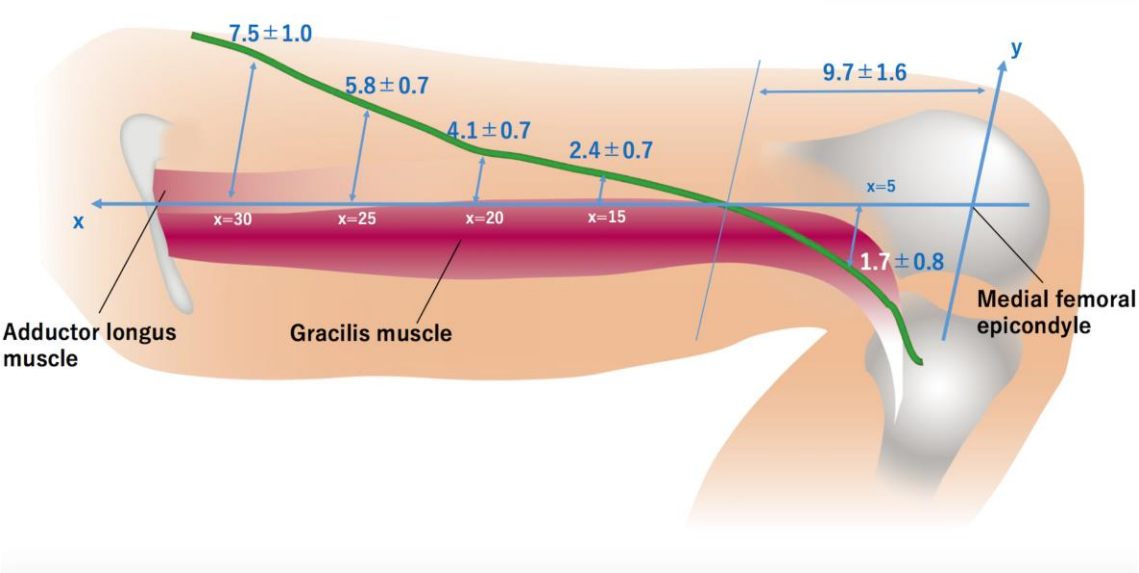


Table 1. Patient data and measurement results (clinical findings)

Patient	Age(yr)	Sex	free of local	Indication	Size (cm)	Pedicle Length (cm)	Anastomosis	Thigh Length(cm)	Intersection of LCV and AGM (cm)	Flap Survival
1	47	Female	free	Breast (Immediate)	9 x 21	6.5	1A2V	30	9	Complete
2	41	Female	free	Breast (Immediate)	9 x 14.5	7	1A1V	32	10	Complete
3	66	Female	free	Breast (Immediate)	9 x 20	6.5	1A2V	31	10.5	Complete
4	49	Female	free	Breast (Immediate)	11 x 15	6	1A2V	32	9	Complete
5	46	Female	free	Breast (Immediate)	13 x 25	9	1A1V	32.5	9.5	Complete
6	43	Female	free	Breast (Immediate)	8 x 17	8	1A2V	31.5	10.5	Complete
7	45	Female	free	Breast (Immediate)	9 x 21	6.5	1A2V	35.5	12	Complete
8	46	Female	free	Breast (Immediate)	11 x 20	4	1A2V	32	6.4	Complete
9	51	Female	free	Breast (Immediate)	10 x 18	7	1A1V	33	8	Complete
10	48	Female	free	Breast (Immediate)	11 x 23	8	1A2V	31	8	Complete
11	41	Female	free	Breast (Immediate)	10 x 24	9	1A1V	31	9.5	Complete
12	54	Female	free	Breast (Immediate)	12 x 25	10	1A1V	34.5	12.5	Complete
13	50	Female	free	Breast (Delayed)	11 x 15	9	1A2V	31.5	9.5	Complete
14	37	Female	free	Breast (Delayed)	7 x 20	10	1A1V	31	10	Complete
15	37	Female	free	Breast (Immediate)	10 x 18	8	1A2V	34	6	Complete
16	43	Male	local	Perineum	9 x 28	n/a	pedicled	35	11	Complete
17	41	Female	free	Breast(Immediate)	9 x 16	8	1A1V	33	10.5	Complete
18	58	Female	free	Breast (delayed)	11 x 15	8.5	1A1V	31	13	Complete
19	54	Female	free	Breast (Immediate)	10 x 18	9	1A1V	32	9.5	Complete
20	40	Female	free	Breast (Immediate)	10 x 16	10	1A2V	31	8.5	Complete
21	44	Male	free	lower limb (sarcoma)	9 x 22.5	6	1A2V	35	10	Complete
22	43	Female	free	Breast (Immediate)	9 x 23	9	1A2V	34	11.5	Complete
23	40	Female	free	Head and Neck (tongue cancer)	6 x 18	8	1A2V	30	10	Complete
24	42	Female	free	Breast (Immediate)	10 x 20	8	1A2V	33	10.5	Complete
Average	46.6				9.7 x 19.7	7.8		32.3	9.7	
SD	6.8				1.5, 3.7	1.5		1.5	1.6	

LCV, Lymph Collecting Vessels; AGM, Anterior edge of Gracilis Muscle



RM12 **Agreement between Perometry and Sequential Girth in Objective Measurement of Leg Volume and Volume Differences**

AC Camargo Cancer Center, São Paulo
Presenter: **Bernardo N Batista, MD, PhD**
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Background: Especially in chronic conditions, such as lymphedema, using proper outcomes to evaluate disease burden and treatment effect is imperative to generate evidence that will guide the best course of action for these lifelong healthcare users. Both for empirical and practical reasons, limb volume and its difference to the contralateral healthy side have been the preferred outcomes studied across lymphedema literature. Overall, the use of sequential girth measurements along the limb (using the formula of a truncated cone to estimate the volume) and perometry have been the most frequently used. We have previously shown that, for arm volume estimation, the measurement error between these two methods was not neglectable and tends to increase as they are mathematically derived to calculate absolute or relative differences between contralateral limbs. **Methods:** We performed bilateral volume estimation in 90 legs of 45 patients being followed for gynecological cancer or leg melanoma treatment with sequential girth measurement every 10 cm, starting at the ankle, and with the use of an automated perometer (perometry). The absolute volume difference between the arms (VD), and the relative difference between them (PEV) were calculated for both methods. **Results:** Correlations between volumes estimated were strong to very strong (r=.66/.68 for right/left leg, r=.9 for VD and r=.9 for PEV). Using the Bland-Altman analysis, we determined that volumes measured by girth were, on average, 420mL smaller than volumes calculated with girth measurement, while their limits of agreement (LOA) ranged from -4.580 to 3.740mL. The LOA represents the range we could expect the volumes to differ between methods, 95% of the times they were performed in the same subject. For VD, LOA was -1.320 to 1.295mL, with a mean difference of -12,6 mL, while PEV had a mean difference of ,4%, with LOA ranging from -22% to 27%. **Conclusion** s: Although they show good correlation, there is considerable measurement error between leg volume estimated by perometry and by sequential girth measurement. Volumes calculated with these methods should be compared with caution. Furthermore, we observed an increasingly relevant measurement bias in outcomes that are derived from leg volumes, originally measured in error.