Global Health & Medicine. 2020; 2(4):227-234.
REVIEW
DOI: 10.35772/ghm.2020.01022

Lymphedema secondary to melanoma treatments: diagnosis, evaluation, and treatments

Azuelos Arié[1,2], Takumi Yamamoto[2,*]

[1] Department of Plastic, Reconstructive, Aesthetic and Maxillofacial Surgery, Henri Mondor University Hospital, Creteil, France;
[2] Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Approximately 300,000 new cases of melanoma are annually diagnosed in the world. Advanced stage melanomas require sentinel lymph node biopsy (SLNB), sometimes lymph node dissections (LND). The development rate of lower extremity lymphedema ranges from 7.6% to 35.1% after inguinal SLNB, and from 48.8% to 82.5% after inguinal LND. Development rate of upper extremity lymphedema ranges from 4.4% to 14.6% after axillary LND. Lymphedema management has constantly improved but effective evaluation and surgical management such as supermicrosurgical lymphaticovenular anastomosis (LVA) are becoming common as minimally invasive lymphatic surgery. Diagnosis and new classification using indocyanine green lymphography allowing pre-clinical secondary lymphedema stage management are improving effectiveness of supermicrosurgical LVA and vascularized lymph node transfer. Lymphatic transfer with lymph-interpositional-flap can restore lymph flow after large oncologic excision even without performing lymphatic anastomosis. Since lymphatic reconstructive surgery may affect local to systemic dissemination of remnant tumor cells, careful consideration is required to evaluate indication of surgical treatments.

***Keywords*:** lymphedema, melanoma, anastomosis, lymph node, supermicrosurgery

Introduction

Melanoma is an aggressive cutaneous cancer affecting 287,723 new patients and responsible for 60,712 deaths in 2018 in the world (*1*). Existence of metastatic regional lymph nodes is one of the most impairing factors on staging and survival prognosis (*2,3*). Sentinel lymph node biopsy (SLNB) is the standard procedure to determine the lymph node metastatic status and, according to the American and European recommendations, complete lymph node dissection (CLND) should be done if the sentinel lymph node is positive (*4,5*).

Despite these recommendations, this procedure is debated due to the morbidity of CLND and the limited oncologic benefit for some patients, but these conclusions are limited by inclusions bias (*6-10*). The SLNB and CLND morbidities are highly attributable to secondary lymphedema and its consequences such as chronic limb swelling responsible for discomfort and functional impairment, recurrent bacterial and fungal infection, ulcerations, psychosocial and cosmetic impairments (*11*). Also, several modifications of surgical technique have been suggested to reduce risk of complications, including preservation of the saphenous vein (*12,13*).

Despite these surgical improvements, lymph node dissections for melanoma treatment still lead to rates between 15.7% and 64.3% of secondary lymphedema (*14-18*). The purpose of this article is to focus on characteristics of secondary lymphedema after melanoma treatment and to report state-of-the-art secondary lymphedema treatments.

Extremity Lymphedema (EL) in melanoma

Lower extremity lymphedema (LEL)

European and American guidelines recommend regional lymph nodes dissection in the treatment of melanoma with positive sentinel lymph node (*4,5*). In the lower limb, the recommended lymphadenectomy is the femoro-inguinal lymph node dissection. SLNB is the standard procedure to determine lymph node metastatic status.

Lower extremity lymphedema (LEL) is the one of the most frequent complication of both SLNB and inguinal lymph node dissection (ILND) in melanoma. Reported rates of LEL secondary to inguinal SLNB were from 7.6% to 35.1% and from 48.8% to 82.5% after ILND (*16,19*). These rates are higher than the LEL rates reported after surgical treatment of advanced

pelvic cancers. According to studies, the LEL rate range after pelvic cancer is between 36.9% and 61% (*20-24*).

LEL in melanoma has a different physiopathology of the LEL secondary to lymphadenectomy for pelvic cancer, which is the cause of a higher rate of LEL. Indeed, American and European guidelines recommend pelvic lymphadenectomy and para-aortic lymphadenectomy in advanced gynecological and prostatic cancer (*25-31*). However, these lymphadenectomies preserve the superficial limb lymph nodes that are removed during the ILND for melanoma. Pelvic and para-aortic lymph node dissection are indirectly responsible for the obstruction of the lower limb superficial lymph flow whereas ILND for melanoma are directly responsible for it. The difference of LEL rates between melanoma and pelvic cancer seems to be due to the difference of lymph node dissection. The wide local excision seems to not be implicated in LEL, no study reported LEL after melanoma excision (*14-16,32*). However, no study compared lymph circulation patterns before and after local wide excision.

Upper extremity lymphedema (UEL)

Axillary lymph node dissection (ALND) is recommended for treatment for both advanced breast cancer and melanoma. The upper extremity lymphedema (UEL) rates after ALND for melanoma were from 4.4% to 14.6% in the reported studies and from 4.1% to 21.4% after ALND for breast cancer (*16-19,33-37*). These two rates are similar probably because the ALND is the same for the both cancers. ALND directly affects the upper limb superficial lymph flows. Also, no study compared lymphatic pattern before and after excision but the fact that these rates are similar is possibly due to the non-implication of wide local excision melanoma in UEL.

Diagnosis

Clinical manifestation of lymphedema

A heaviness sensation of the limb is the first manifestation of extremity lymphedema (EL). Extremity discomfort, tension, pain or tingling sensations can also be felt mostly during the evening. Edema can affect one, two or three limb parts depending on the EL stage. Other causes of edema such as heart failure, hepatic failure, nephrotic syndrome, cancer and venous insufficiency have to be excluded. In severe cases, EL can be associated with acute skin infections such as cellulitis and chronic inflammation causing skin thickening, interstitial tissue fibrosis, hyperkeratosis, and/or chronic ulcerations.

The International Society of Lymphology classification is based on physical condition of the extremities (*38*). Stage 0 refers to a latent or subclinical lymphedema without swelling. Stage I represents an early accumulation of fluid relatively high in protein content which subsides with limb elevation. Stage II signifies that limb elevation alone rarely reduces the tissue swelling and pitting is manifested except in late stage II when fibrosis is developed. Stage III encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes are seen.

Imaging

Complementary imaging examinations in both primary and secondary lymphedema are fundamental. They help to confirm the diagnosis by showing involvement of a pathologic lymphatic system in edema, they allow to stage lymphedema and to schedule surgical procedures.

Indocyanine green (ICG) lymphography

ICG lymphography is used to study the superficial lymphatic system. Using a near infrared fluorescence camera, subcutaneously or intradermally injected ICG shows enhancement of fluorescent image of superficial lymph circulation up to 2 cm from the skin surface in real time. More related to the pathogenic mechanism of lymphedema, ICG lymphography severity staging has been developed based on the anatomy and the functional superficial lymphatic vessels as seen in ICG lymphography (Table 1) (*39*). Four patterns of ICG lymphography findings are correlated with clinical stage. Linear pattern (Figure 1A) is related to normally functional superficial lymphatic collectors. When lymph flows are obstructed, the lymphatic collectors become dilated, leading to retrograde lymph flows called dermal backflow.

The first and less severe dermal backflow pattern is the splash pattern (Figure 1B) that is correlated with lymphatic reflux into the more superficial collecting and precollecting lymphatic vessels, showing tortuous lines on ICG lymphography. The second dermal backflow pattern is the stardust pattern (Figure 1C) correlated

Table 1. Pathophysiolgical severity stage based on ICG lymphography findings

ICG stage	Lymphography findings	Clinical conditions
stage 0	Linear pattern only (no DB pattern)	No lymphedema
stage I	Splash pattern (+ Linear pattern)	Subclinical lymphedema
stage II	SD pattern in 1 region (+ Linear pattern)	Early lymphedema
stage III	SD pattern in 2 region (+ Linear pattern)	Progressed lymphedema
stage IV	SD pattern in 3 region (+ Linear pattern)	
stage V	SD pattern only (no Linear pattern)	

Upper/lower extremity can be divided into 3 regions; the upper-arm/thigh, the forearm/lower-leg, and the hand/foot. ICG, indocyanine green; DB, dermal backflow; SD, Stardust and/or Diffuse.

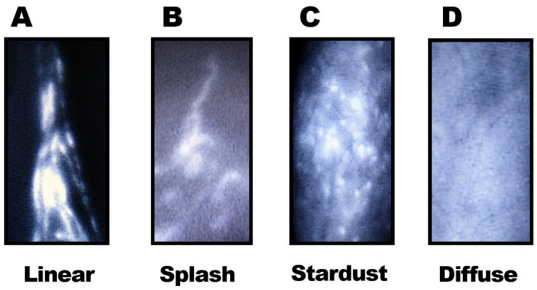

Figure 1. Characteristic ICG lymphography patterns. (A) Linear pattern; **(B)** Splash pattern; **(C)** Stardust pattern; **(D)** Diffuse pattern. Lymphographic pattern changes from Linear to Splash, Stardust, and finally to Diffuse pattern with progression of lymphedema.

with lymphatic reflux into the precollecting lympahtic vessels flowing vertically to the dermal capillary lympahtics, showing spots on ICG lymphography. The most severe dermal backflow is the diffuse pattern (Figure 1D) related to lymph flows in the dilated dermal lymphatic capillaries, showing a diffusely enhanced area on ICG lymphography (*40-44*).

Lymphoscintigraphy

Lymphoscintigraphy is described as the principal examination to perform in lymphedema. Lymphoscintigraphy can be used to study the superficial and deep lymphatic system whereas ICG lymphography can only study the superficial lymphatic system. Lymphoscintigraphy informs about qualitative and quantitative functional parameters of the lymphatic system. Normal lymphoscintigraphy shows normal superficial and deep lymphatic vessels and lymph nodes as part of these pathways. Abnormal lymphoscintigraphy can show, lack of lymphatic vessels (superficial or deep), lack of lymphatic nodes, post-obstruction reflux into the lymphatic collateral network or dermal backflow (diffuse tracer repartition) in one part of the limb or through the whole limb. Axillary or groin lymphorrhea can be observed after lymph node dissection, slow (persistence of tracer activity) or incomplete lymphatic drainage. Some authors reported lymphoscintigraphy based classifications to select the most appropriate surgical treatment (*45*).

Single photon emission computed tomography-computerized tomography (SPECT-CT) lymphography and Magnetic Resonance Lymphography (MRL)

SPECT-CT lymphography and MRL can also give information about superficial and deep lymphatic systems. One of the most interesting advantages is that they can give volumetric details and localize superficial and deep lymphatic channels seen as linear or tortuous vessels and lymph nodes (*46*). They can also give precise localization and function of the collateral network. Contrast diffusion can, as in ICG lymphography, reveal dermal backflow. However, injections are required and, recurrent irradiation in post-cancer patients should be limited. Moreover, regarding lymphatic disease progression or post-surgical evolution and their availability, some centers cannot afford to repeat these examinations.

Lymphedema management

Non-surgical Management

Medical management

No medical treatment is indicated in routine management of lymphedema however, some studies reported an effect of medical treatment on EL. Results of studies focusing on coumarin, diosmin and arbutin are contrasted and, due to hepatotoxicity, there is no recommendation for routine use (*47,48*). Diuretics are considered a contraindication. Antibiotics are recommended to prevent recurrence of limb cellulitis but are not effective for lymphedema. The overuse of antibiotics increases the risk of emergence of multi-drug resistant bacterial infection.

Decongestive therapy

Physiotherapeutic management of EL has been reported to be effective. Studies proved that pneumatic compression are effective on EL (*49-52*). Treatment of lymphedema with complete decongestive physiotherapy (CDT), which combines manual lymphatic drainage, lymphedema rehabilitation exercises, compression therapy, and skin care, can achieve a 45-70% reduction in EL volume (*48-50*). Phase 1 of CDT consists of skin care and manual lymphatic drainage. Phase 2 consists of compression, manual drainage and exercises to conserve the benefit obtained in phase 1.

Magnetotherapy and electrotherapy have also shown good results (*53*). Intermittent pneumatic compression has shown good results but only a few studies have been published. It is understood that compression therapy used in CDT is effective in EL treatment but has to be adapted so as not to reduce the quality of life (*54-56*). Thermal therapy, aquatherapy, low-level laser therapy and ultrasounds therapy have also been suggested.

All of this non-surgical management is anti-symptomatic treatment and not curative, because it cannot restore lymph flow. Therefore, life-long treatment is required.

Surgical management

EL surgical treatment includes several procedures which can be separated into two groups: physiological and ablative surgeries. Physiological surgeries aim to restore lymph drainage to the lymphatic system, venous system or new lymphatic pathways after lymphangiogenesis

whereas ablative surgeries remove affected tissues (*36,57-59*). Physiological surgeries are so classified:

• Lymphatic bypasses which aim to divert congested lymph to intact lymphatic or venous circulation. They can be classified into lymphatico-lympahtic bypass, lymphatico-venous implantation, lymph node to vein shunt and lymphaticovenular anastomosis.

• Lymphatic transfers from a healthy lymphatic donor site. They include vascularized lymph node transfer with or without efferent lymphatic vessel anastomosis, and lymph-interpositional-flap transfer (LIFT).

Lymphatic bypass

Lymphatico-lymphatic bypass: Lymphatic to lymphatic bypass, using a lymphatic graft seems more physiologic. It has been reported on a 329 patient series that more than 60% of the patients with UEL showed a reduction in volume difference to the healthy side of more than 50% after a mean follow-up period of more than 2 years (*60*). However, this technique is invasive for the donor site with a risk of lymphedema on the donor site.

Lymph node to vein anastomosis and lymph node implantation: The implantation uses microsurgical techniques to insert lymphatic vessels into a vein. Some authors reported good results but the thrombosis risk is higher than in supermicrosurgical lymphaticovenular anastomosis (LVA) because the lymphatic vessel adventitia is in contact with the venous lumen (*61-63*). Serious complications such as deep venous thrombosis and pulmonary embolism were reported. Because of high risk of thrombosis and possibility of serious sequelae, this procedure has been abandoned by most lymphatic surgeons.

Supermicrosurgical lymphaticovenular anastomosis (LVA): Unlike the above mentioned classical lymphovenous shunt operations, supermicrosurgical LVA creates a real anastomosis of lymphatic vessel to recipient venule or small vein in an intima-to-intima coaptation manner. Since lymphatic vessels can be smaller than 0.5 mm, supermicrosurgical techniques which allow anastomosis of vessels with an external diameter of 0.5 mm or smaller, is necessary to perform LVA surgery. LVA are an anastomosis between a superficial lymphatic vessel (mostly under the superficial fascia) and a superficial vein. Supermicrosurgical anastomosis allows intima-to-intima coaptation even when vessel diameters are smaller than 0.5 mm.

LVA is performed in an end-to-end, side-to-end, side-to-side, or end-to-side fashion. Various anastomotic configurations can be combined to maximize lymph flow drainage. Lambda-shaped LVA allows bidirectional bypass using a lymphatic vessel and a vein with end-to-end and end-to-side anastomosis (*64-72*). LVA is the least invasive surgery to treat lymphedema. It can be performed under local anesthesia through an approximately 2 cm incision allowing for day surgery.

Lymphatic transfer

Vascularized lymph node transfer (VLNT): VLNT is a reconstructive lymphatic surgery mainly for advanced cases where lumen of lymphatic vessels are obstructed because of lymphosclerosis or patients where lymphatic vessels are not found. VLNT requires less technically demanding procedures, since supermicrosurgy is not basically needed (*73,74*). Supermicrosurgery is required, when the efferent lymphatic vessel of a transferred lymph node is anastomosed (*58*).

Two different mechanisms are suggested to explain VLNT effects. The first one is that VLNT would act like a bridge over the obstruction zone because the VLNT flap contains many functional lymphatic vessels and nodes. Therefore, the VLNT flap has to be large enough to reach both beyond the obstruction, and to reconnect lymphatics on both sides *via* lymphangiogenesis (*74*). The other mechanism is that the VLNT flap would act like a lymphatic pump to the blood circulation (*75*). Several donor sites have been identified; inguinal, lateral thoracic, supraclavicular submental and omentum. On a literature review of about 271 VLNT cases (24 studies), Scaglioni *et al.* reported that submental VLNT were the most effective with 100% of patients showing improvement, the supraclavicular was the second highest rate of benefit (88.2%), followed by the inguinal VLNT (70.4%, n =138), 60% of omental VLNT demonstrated benefit, and only 5% of lateral thoracic VLNT reported an improvement. The highest complication rate on donor site was on lateral thoracic (15.8%), then in inguinal (10.9%), supraclavicular (1.2%) and submental (0%) and omentum (0%). Donor site lymphedema was more frequent in lateral thoracic (13.2%) and inguinal (1.6%). No donor site lymphedema was reported on supraclavicular, submental or omentum.

Lymph-interpositional-flap transfer (LIFT): Traumatic lesions and oncologic excisions can interrupt lymphatic flow and lead to lymphedema. A retrospective study suggested that tissue replantation or reconstruction could restore lymph flow without lymph node transfer or lymphatic vessel anastomosis (*59*). This study showed that spontaneous lymph flow restoration depended on compatible lymph axiality without raw surface in lymph axiality. When lymphatic vessel stumps in a recipient site and transferred tissue were approximated to each other, the lymphatic vessels could be reconnected spontaneously without supermicrosurgical lymphatic anastomosis. Based on the concept of lymph axiality, a new lymphatic reconstruction, LIFT, has been developed, allowing lymph flow reconstruction without supermicrosurgical technique or lymph node sacrifice. Since LIFT does not sacrifice lymph nodes at the donor site, donor site lymphedema risk is significantly reduced unlike VLNT.

For LIFT operation, ICG lymphography is necessary to precisely localize lymphatic vessels both in a donor flap and a recipient site. Linear patterns from flaps were

aligned as best possible to the donor site linear patterns under ICG lymphography surgical navigation. LIFT can be applied for primary prevention of lymphedema in oncological ablative surgery and for treatment of established secondary lymphedema.

Debulking surgeries: resection and liposuction

Chronic lymphedema is responsible for damaging soft tissues and leads to a dermato-lipofibrosclerosis. Patients with severe stage lymphedema can be affected by recurrent fungal and bacteriologic infections, as well as elephantiasis and have a deformed extremity limiting compression effectiveness. Once fat deposition and fibrotic histopathological changes occur, reconstructive surgery cannot improve the changes, and some debulking procedures may be required to improve the established histopathologic changes. Unlike lymphatic reconstructive surgery, debulking surgeries aim to decrease lymphedematous volume directly by removing the lymphedematous tissue, allowing an immediate affect of volume reduction. However, debulking procedures destroy the remaining lymphatic structures, and worsen lymph circulation. Therefore, even stronger compression treatment is required after some debulking surgeries.

Charles' procedure was a surgical excision management described in 1912. The treated limb part (thigh or thigh+leg) is circumferentially denuded down to the deep fascia. The deep fascia thickness is also reduced to a normal size. The excised tissue is used as a donor site for split thickness skin graft. Feins described a Hofman's procedure. Skin incision is done from up to down in the affected limb. Two skin flaps are harvested. Lymphadematous tissues from subcutaneous fat to deep fascia are excised. After hemostasis, skin flaps are replaced on muscles. Depending on volume excess, this procedure can be repeated (*76*). Some authors describe improvement of clinical conditions and quality of life after excisional surgery or liposuction on severe lymphedematous patients (*77,78*). This type of surgery should be considered only after failure of all physiologic treatments and only when patient's compliance for maximum compression therapy is confirmed, because lymphedematous tissues shall re-increase as lymph circulation is even further deteriorated after debulking procedures; debulking procedures can also be destructive to remaining lymphatic functions.

Conclusion

Secondary limb lymphedema after SLNB or CLND for melanoma affects a high percentage of patients and lymphatic follow-up should systematically be considered. Lymphatic surgeries after melanoma may present a possible risk to accelerate dissemination of a local melanoma recurrence, which should be well evaluated before performing lymphatic surgeries.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394-424.
2. Coit DG, Thompson JA, Algazi A, *et al*. NCCN Guidelines Insights: Melanoma, Version 3.2016. J Natl Compr Cancer Netw. 2016; 14:945-958.
3. Balch CM, Gershenwald JE, Soong S-J, *et al*. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27:6199-6206.
4. Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U, ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5:v126-132.
5. Nguyen B, Karia PS, Hills VM, Besaw RJ, Schmults CD. Impact of National Comprehensive Cancer Network Guidelines on Case Selection and Outcomes for Sentinel Lymph Node Biopsy in Thin Melanoma. Dermatol Surg. 2018; 44:493-501.
6. Leiter U, Stadler R, Mauch C, *et al.* Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016; 17:757-767.
7. Faries MB, Thompson JF, Cochran AJ, *et al.* Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017; 376:2211-2222.
8. Poos HP, Kruijff S, Bastiaannet E, van Ginkel RJ, Hoekstra HJ. Therapeutic groin dissection for melanoma: risk factors for short term morbidity. Eur J Surg Oncol. 2009; 35:877-883.
9. Postlewait LM, Farley CR, Seamens AM, Le N, Rizzo M, Russell MC, Lowe MC, Delman KA. Morbidity and outcomes following axillary lymphadenectomy for melanoma: weighing the risk of surgery in the era of MSLT-II. Ann Surg Oncol. 2018; 25:465-470.
10. Masoud SJ, Perone JA, Farrow NE, Mosca PJ, Tyler DS, Beasley GM. Sentinel lymph node biopsy and completion lymph node dissection for melanoma. Curr Treat Options Oncol. 2018; 19:55.
11. Grada AA, Phillips TJ. Lymphedema: pathophysiology and clinical manifestations. J Am Acad Dermatol. 2017; 77:1009-1020.
12. Baur J, Mathe K, Gesierich A, Weyandt G, Wiegering A, Germer CT, Gasser M, Pelz JOW. Morbidity and oncologic outcome after saphenous vein-sparing inguinal lymphadenectomy in melanoma patients. World J Surg Oncol. 2017; 15:99.
13. Oztürk MB, Akan A, Ozkaya O, Egemen O, Oreroğlu AR, Kayadibi T, Akan M. Saphenous vein sparing superficial inguinal dissection in lower extremity melanoma. J Skin Cancer. 2014; 2014:652123.
14. Palmer PE 3rd, Warneke CL, Hayes-Jordan AA, Herzog CE, Hughes DP, Lally KP, Austin MT. Complications in the surgical treatment of pediatric melanoma. J Pediatr Surg. 2013; 48:1249-1253.
15. de Vries M, Vonkeman WG, van Ginkel RJ, Hoekstra HJ. Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma. Eur J Surg Oncol. 2006; 32:785-789.

16. Jørgensen MG, Toyserkani NM, Thomsen JB, Sørensen JA. Surgical-site infection following lymph node excision indicates susceptibility for lymphedema: A retrospective cohort study of malignant melanoma patients. J Plast Reconstr Aesthetic Surg. 2018; 71:590-596.
17. Gjorup CA, Groenvold M, Hendel HW, Dahlstroem K, Drzewiecki KT, Klausen TW, Hölmich LR. Health-related quality of life in melanoma patients: impact of melanoma-related limb lymphoedema. Eur J Cancer. 2017; 85:122-132.
18. Ahmed A, Sadadcharam G, Huisma F, Fogarty K, Mushtaque M, Shafiq A, Redmond P. Postoperative complications following nodal dissection and their association with melanoma recurrence. ISRN Surg. 2013; 2013: 382138.
19. Gjorup CA, Hendel HW, Zerahn B, Dahlstroem K, Drzewiecki KT, Klausen TW, Hölmich LR. Volume and tissue composition changes measured with dual-energy X-ray absorptiometry in melanoma-related limb lymphedema. Lymphat Res Biol. 2017; 15:274-283.
20. Kuroda K, Yamamoto Y, Yanagisawa M, Kawata A, Akiba N, Suzuki K, Naritaka K. Risk factors and a prediction model for lower limb lymphedema following lymphadenectomy in gynecologic cancer: a hospital-based retrospective cohort study. BMC Womens Health. 2017; 17:50.
21. Tanaka T, Ohki N, Kojima A, Maeno Y, Miyahara Y, Sudo T, Takekida S, Yamaguchi S, Sasaki H, Nishimura R. Radiotherapy negates the effect of retroperitoneal nonclosure for prevention of lymphedema of the legs following pelvic lymphadenectomy for gynecological malignancies: an analysis from a questionnaire survey. Int J Gynecol Cancer. 2007; 17:460-464.
22. Volpi L, Sozzi G, Capozzi VA, Ricco' M, Merisio C, Di Serio M, Chiantera V, Berretta R. Long term complications following pelvic and para-aortic lymphadenectomy for endometrial cancer, incidence and potential risk factors: a single institution experience. Int J Gynecol Cancer. 2019; 29:312-319.
23. Lindqvist E, Wedin M, Fredrikson M, Kjølhede P. Lymphedema after treatment for endometrial cancer - A review of prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol. 2017; 211:112-121.
24. Salehi S, Åvall-Lundqvist E, Brandberg Y, Johansson H, Suzuki C, Falconer H. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 2019; 29:86-93.
25. Parker C, Gillessen S, Heidenreich A, Horwich A; ESMO Guidelines Committee. Cancer of the prostate: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5:v69-77.
26. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N; ESMO Guidelines Committee. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4):iv262.
27. Colombo N, Sessa C, Bois A du, *et al.* ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019; ijgc-2019-000308.
28. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Radiother Oncol. 2015; 117:559-581.
29. Chuang LT, Temin S, Camacho R, *et al.* Management and care of women with invasive cervical cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline. J Glob Oncol. 2016; 2:311-340.
30. Preisser F, Mazzone E, Nazzani S, Marchioni M, Bandini M, Tian Z, Saad F, Soulières D, Shariat SF, Montorsi F, Huland H, Graefen M, Tilki D, Karakiewicz PI. North American population-based validation of the National Comprehensive Cancer Network Practice Guideline Recommendations for locoregional lymph node and bone imaging in prostate cancer patients. Br J Cancer. 2018; 119:1552-1556.
31. Morgan RJ Jr, Armstrong DK, Alvarez RD, *et al.* Ovarian Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw. 2016; 14:1134-1163.
32. Banting S, Milne D, Thorpe T, Na L, Spillane J, Speakman D, Henderson MA, Gyorki DE. Negative sentinel lymph node biopsy in patients with melanoma: the patient's perspective. Ann Surg Oncol. 2019; 26:2263-2267.
33. Faries MB, Thompson JF, Cochran A, *et al.* The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the Multicenter Selective Lymphadenectomy Trial (I). Ann Surg Oncol. 2010; 17:3324-3329.
34. Tummel E, Ochoa D, Korourian S, Betzold R, Adkins L, McCarthy M, Hung S, Kalkwarf K, Gallagher K, Lee JY, Klimberg VS. Does axillary reverse mapping prevent lymphedema after lymphadenectomy? Ann Surg. 2017; 265:987-992.
35. Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N, Koshima I. Split intravascular stents for side-to-end lymphaticovenular anastomosis. Ann Plast Surg 2013; 71:538-540.
36. Coen JJ, Taghian AG, Kachnic LA, Assaad SI, Powell SN. Risk of lymphedema after regional nodal irradiation with breast conservation therapy. Int J Radiat Oncol Biol Phys. 2003; 55:1209-1215.
37. Mathew J, Barthelmes L, Neminathan S, Crawford D. Comparative study of lymphoedema with axillary node dissection versus axillary node sampling with radiotherapy in patients undergoing breast conservation surgery. Eur J Surg Oncol. 2006; 32:729-732.
38. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020; 53:3-19.
39. Yamamoto T, Narushima M, Doi K, Oshima A, Ogata F, Mihara M, Koshima I, Mundinger GS. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: the generation of a novel lymphedema severity staging system using dermal backflow patterns. Plast Reconstr Surg. 2011; 127:1979-1986.
40. Yamamoto T, Yamamoto N, Yoshimatsu H, Hayami S, Narushima M, Koshima I. Indocyanine green lymphography for evaluation of genital lymphedema in secondary lower extremity lymphedema patients. J Vasc Surg Venous Lymphat Disord. 2013; 1:400-405.e1.
41. Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N,

Hayashi A, Koshima I. Indocyanine green lymphography findings in primary leg lymphedema. Eur J Vasc Endovasc Surg. 2015; 49:95-102.
42. Yamamoto T, Yamamoto N, Doi K, Oshima A, Yoshimatsu H, Todokoro T, Ogata F, Mihara M, Narushima M, Iida T, Koshima I. Indocyanine green–enhanced lymphography for upper extremity lymphedema: a novel severity staging system using dermal backflow patterns. Plast Reconstr Surg. 2011; 128:941-947.
43. Yamamoto T, Matsuda N, Doi K, Oshima A, Yoshimatsu H, Todokoro T, Ogata F, Mihara M, Narushima M, Iida T, Koshima I. The earliest finding of indocyanine green lymphography in asymptomatic limbs of lower extremity lymphedema patients secondary to cancer treatment: the modified dermal backflow stage and concept of subclinical lymphedema. Plast Reconstr Surg. 2011; 128:314e-321e.
44. Yamamoto T, Narushima M, Yoshimatsu H, Yamamoto N, Oka A, Seki Y, Todokoro T, Iida T, Koshima I. Indocyanine green velocity: lymph transportation capacity deterioration with progression of lymphedema. Ann Plast Surg. 2013; 71:591-594.
45. Yamamoto T, Chen WF, Yamamoto N, Yoshimatsu H, Tashiro K, Koshima I. Technical simplification of the supermicrosurgical side-to-end lymphaticovenular anastomosis using the parachute technique. Microsurgery. 2015; 35:129-134.
46. Yamamoto T, Yamamoto N, Kageyama T, Sakai H, Fuse Y, Tsuihiji K, Tsukuura R. Technical pearls in lymphatic supermicrosurgery. Global Health & Medicine. 2020; 2:29-32.
47. Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N, Shim TWH, Seki Y, Kikuchi K, Karibe J, Azuma S, Koshima I. Sequential anastomosis for lymphatic supermicrosurgery: multiple lymphaticovenular anastomoses on 1 venule. Ann Plast Surg. 2014; 73:46-49.
48. Garza R, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. BMC Cancer. 2017; 17:468.
49. Phillips JJ, Gordon SJ. Intermittent pneumatic compression dosage for adults and children with lymphedema: a systematic review. Lymphat Res Biol. 2019; 17:2-18.
50. Bergan JJ, Sparks S, Angle N. A comparison of compression pumps in the treatment of lymphedema. Vasc Surg. 1998; 32:455-462.
51. Yamamoto T, Yamamoto N, Yamashita M, Furuya M, Hayashi A, Koshima I. Efferent lymphatic vessel anastomosis (ELVA): supermicrosurgical efferent lymphatic vessel-to-venous anastomosis for the prophylactic treatment of subclinical lymphedema. Ann Plast Surg. 2016; 76:424-427.
52. Yamamoto T, Yamamoto N, Yoshimatsu H, Narushima M, Koshima I. Factors associated with lymphosclerosis: an analysis on 962 lymphatic vessels. Plast Reconstr Surg 2017; 140:734-741.
53. Yamamoto T, Narushima M, Koshima I. Lymphatic vessel diameter in female pelvic cancer-related lower extremity lymphedematous limbs. J Surg Oncol. 2018; 117:1157-1163.
54. Pugh S, Stubbs C, Batchelor A. Managing upper limb lymphoedema with use of a combined armsleeve compression garment. Br J Community Nurs. 2017; 22(Sup10):S38-S43.
55. Yamamoto T, Yamamoto N, Yoshimatsu H, Narushima M, Koshima I. Factors associated with lower extremity dysmorphia caused by lower extremity lymphedema. Eur J Vasc Endovasc Surg. 2017; 54:126.
56. Miller A. Impact of seamless compression garments on limb functionality, comfort and quality of life. Br J Community Nurs. 2017; 22(Sup10):S26-S37.
57. Brahma B, Yamamoto T. Breast cancer treatment-related lymphedema (BCRL): An overview of the literature and updates in microsurgery reconstructions. Eur J Surg Oncol. 2019; 45:1138-1145.
58. Yamamoto T, Yoshimatsu H, Yamamoto N. Complete lymph flow reconstruction: A free vascularized lymph node true perforator flap transfer with efferent lymphaticolymphatic anastomosis. J Plast Reconstr Aesthet Surg. 2016; 69:1227-1233.
59. Yamamoto T, Iida T, Yoshimatsu H, Fuse Y, Hayashi A, Yamamoto N. Lymph flow restoration after tissue replantation and transfer: importance of lymph axiality and possibility of lymph flow reconstruction without lymph node transfer or lymphatic anastomosis. Plast Reconstr Surg. 2018; 142:796-804.
60. Yamamoto T. Near-infrared fluorescent lymphography. In: Lymphedema: A Concise Compendium of Theory and Practice. 2nd edition. (Lee BB, Rockson SG, Bergan J. eds.) Springer Berlin, Heidelberg, Germany, 2017; pp. 346-355
61. Ishiura R, Yamamoto T, Siato T, Mito D, Iida T. Comparison of lympho-venous shunt methods in rat model: spermicrosurgical lymphaticovenular anastomosis versus microsurgical lymphaticovenous implantation. Plast Reconstr Surg 2017; 39:1407-13.
62. Nacchiero E, Maruccia M, Vestita M, Elia R, Marannino P, Giudice G. Multiple lymphatic-venous anastomoses in reducing the risk of lymphedema in melanoma patients undergoing complete lymph node dissection. A retrospective case-control study. J Plast Reconstr Aesthetic Surg. 2019; 72:642-648.
63. Boccardo F, Casabona F, De Cian F, Friedman D, Murelli F, Puglisi M, Campisi CC, Molinari L, Spinaci S, Dessalvi S, Campisi C. Lymphatic microsurgical preventing healing approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: over 4 years follow-up. Microsurgery. 2014; 34:421-424.
64. Yamamoto T, Narushima M, Kikuchi K, Yoshimatsu H, Todokoro T, Mihara M, Koshima I. Lambda-shaped anastomosis with intravascular stenting method for safe and effective lymphaticovenular anastomosis. Plast Reconstr Surg. 2011; 127:1987-1992.
65. Fuse Y, Yamamoto T. Half notching method for supermicrosurgical lambda-shaped lymphaticovenular anastomosis. J Plast Reconstr Aesthetic Surg. 2016; 69:e13-14.
66. Yamamoto T. Comment: selection of anastomosis type for lymphaticovenular anastomosis. J Plast Reconstr Aesthetic Surg. 2013; 66:207-208.
67. Yamamoto T, Yoshimatsu H, Narushima M, Seki Y, Yamamoto N, Shim TW, Koshima I. A modified side-to-end lymphaticovenular anastomosis. Microsurgery. 2013; 33:130-133.
68. Phillips GSA, Gore S, Ramsden A, Furniss D. Lymphaticovenular anastomosis in the treatment of secondary lymphoedema of the legs after cancer treatment. J Plast Reconstr Aesthetic Surg. 2019; 72:1184-1192.
69. Yamamoto T, Yoshimatsu H, Yamamoto N, Narushima

M, Iida T, Koshima I. Side-to-end lymphaticovenular anastomosis through temporary lymphatic expansion. PloS One. 2013; 8:e59523.
70. Winters H, Tielemans HJP, Verhulst AC, Paulus VAA, Slater NJ, Ulrich DJO. The long-term patency of lymphaticovenular anastomosis in breast cancer-related lymphedema. Ann Plast Surg. 2019; 82:196-200.
71. Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. J Reconstr Microsurg. 2000; 16:437-442.
72. Basta MN, Gao LL, Wu LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. Plast Reconstr Surg. 2014; 133:905-913.
73. Yamamoto T, Yamamoto N, Yoshimatsu H, Narushima M, Koshima I. Factors associated with lymphosclerosis: an analysis on 962 lymphatic vessels. Plast Reconstr Surg. 2017; 140:734-741.
74. Tourani SS, Taylor GI, Ashton MW. Vascularized lymph node transfer: a review of the current evidence. Plast Reconstr Surg. 2016; 137:985-993.
75. Scaglioni MF, Arvanitakis M, Chen YC, Giovanoli P, Chia-Shen Yang J, Chang EI. Comprehensive review of vascularized lymph node transfers for lymphedema: Outcomes and complications. Microsurgery. 2018; 38:222-229.
76. Vignes S. Complex decongestive therapy. In: Lymphedema: Presentation, Diagnosis, and Treatment. (Gren AK, Slavin SA, Brorson H. eds.) Springer Cham, Heidelberg, Germany, 2015; pp. 227-236.
77. Lee BB, Kim YW, Kim DI, Hwang JH, Laredo J, Neville R. Supplemental surgical treatment to end stage (stage IV-V) of chronic lymphedema. Int Angiol. 2008; 27:389-395.
78. Brorson H. Liposuction in arm lymphedema treatment. Scand J Surg. 2003; 92:287-295.

Received April 9, 2020; Revised July 22, 2020; Accepted July 29, 2020.

Released online in J-STAGE as advance publication August 2, 2020.

*_Address correspondence to_:
Takumi Yamamoto, Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: tyamamoto-tky@umin.ac.jp