Lymphology 57 (2024) 211-218

CHARACTERISTIC SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY-COMPUTED TOMOGRAPHY (SPECT-CT) FINDINGS IN SECONDARY GENITAL LYMPHEDEMA

S. M. Ohki, H. Sakai, T. Miyazaki, R. Tsukuura, T. Yamamoto

Department of Medical Education, National Center for Global Health and Medicine, Tokyo, Japan (SMO); Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan (HS, TM, RT, TY).

ABSTRACT

Diagnosis and evaluation of genital lymphedema (GL) is a challenging yet crucial step in the treatment of GL. Single photon emission computed tomography-computed tomography (SPECT-CT) is useful for lymph flow imaging, but its characteristic findings for GL are not clarified. The purpose of this study was to uncover characteristic SPECT-CT findings in secondary GL. Medical records of patients who underwent SPECT-CT and indocyanine (ICG) lymphography for evaluation of secondary lower extremity lymphedema (LEL) and/or genital lymphedema (GL) were reviewed. Characteristic SPECT-CT findings were identified based on timing, visibility, and extension of lymphatic enhancement in the lower abdominal, inguinal, genital, and pelvic regions. Patients were divided into either GL group with genital ICG lymphography stage I-V or control group with stage 0. Prevalence of each SPECT-CT finding was compared between the groups. Ten female patients were included; 7 (70%) were classified in GL group, and 3 (30%) in control group. Characteristic SPECT-CT findings included pauci-enhancement of inguinal lymph nodes (PEIL), genital dermal back flow, external iliac lymph nodes non-enhancement, common iliac lymph nodes non-enhancement, and periaortic lymph nodes non-enhancement. There was a statistically significant difference between GL and control groups for PEIL (100% vs. 0%, P = 0.002). Characteristic SPECT-CT findings in secondary GL were identified. Further studies are warranted to clarify usefulness of the findings for management of GL.

Keywords: SPECT-CT; genital lymphedema; ICG lymphography; diagnosis

INTRODUCTION

Genital lymphedema (GL) is a chronic and debilitating condition caused by dysfunctional lymphatic transportation of the genital-pubic region. GL is an important comorbidity of secondary lower extremity lymphedema (LEL), of which is usually caused by pelvic cancer treatment (1,2). Female GL can cause discomfort, urinary problems, and eventually lymphorrhea (3). Treatment of GL is particularly challenging because it is difficult to apply effective compression to the genital areas unlike the lower limbs (4-6).

Early diagnosis is key to avoiding deterioration of GL (5). However, there are still deficiencies in early detection of GL despite the advent of various imaging modalities (7-16). The current gold-standard for lymphedema diagnosis is lymphoscintigraphy (14,15). However, lymphoscintigraphy has poor tomographic

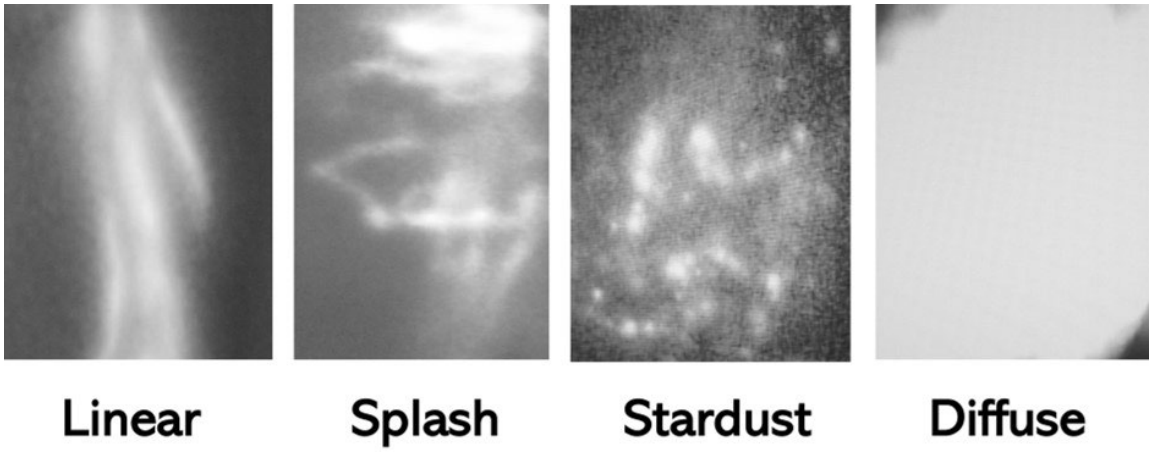

Fig. 1. *Characteristic ICG lymphography findings include a normal "Linear" pattern, and abnormal "Splash", "Stardust", and "Diffuse" patterns.*

and temporal resolution (15). For GL in particular, the accumulation of radioisotopes in the bladder can obscure visualization of the genital areas. In the past decade, indocyanine green (ICG) lymphography has become an indispensable tool in lymphedema, for its ability to diagnose preclinical states, and its usefulness in surgical intervention (17-19). Severity grading scheme for GL based on ICG lymphography findings is becoming popular, but cannot be applied where a near-infrared camera is not available (20,21). Therefore, ICG evaluation of asymptomatic GL cases is usually not routine, potentially leading to missed treatment opportunities. Recently, single-photon emission computed tomography-computed tomography (SPECT-CT) has seen increasing use in the evaluation of lymphedema (13). Advantages of SPECT-CT are three-dimensional visualization of lymph flow, including deep intrapelvic and abdominal flows, and temporal visualization by obtaining sequential images (15). Thus, SPECT-CT provides distinct advantages over both ICG lymphography and lymphoscintigraphy. Since SPECT-CT can be performed with the same radioisotope tracers and protocols used in lymphoscintigraphy, it should be readily available to facilities with SPECT-CT imagers and prior experience with lymphoscintigraphy.

Despite recent popularity, characteristic SPECT-CT findings for GL have not been well studied. There are no studies comparing SPECT-CT findings of GL to reliable controls, specifically none comparing SPECT-CT findings to those of ICG lymphography. Because ICG lymphography is capable of accurate and early diagnosis of GL, identifying SPECT-CT findings that correlate well with ICG findings is especially important. The purpose of this study was to uncover characteristic SPECT-CT findings in secondary GL

METHODS

Electronic medical records of patients who underwent both ICG lymphography and SPECT-CT for evaluation of secondary LEL and/or GL from July 2020 to April 2021 were reviewed. The exclusion criteria included patients with other edematous diseases, and patients with history of surgery for lymphedema. ICG lymphography was performed as previously reported, and genital ICG lymphography stage was determined based on the findings (*Fig. 1 & Table 1*) (20). Patients with genital ICG lymphography stage I-V were classified in GL group, and those with genital ICG lymphography stage 0 in control group.

SPECT-CT was performed as previously reported; Tc^{99m}-phytate 150-185 MBq, 0.3mL

TABLE 1
Genital ICG Lymphography Stage for GL Evaluation

ICG stage	ICG lymphography findings
stage 0	Linear only (no dermal backflow)
stage I	Linear + Splash
stage II	Linear + Stardust/Diffuse (1 region)*
stage III	Linear + Stardust/Diffuse (2 region)*
stage IV	Linear + Stardust/Diffuse (3 region)*
stage V	Stardust/Diffuse only (no Linear)

* The genitalia is divided into 3 regions; the lower abdomen, the labia majora, and the labia minora. ICG, indocyanine green. GL, genital lymphedema

in total, was subcutaneously injected into the first interdigital spaces of the both feet (22,23). Afterwards, images were acquired using a low-energy-high-resolution collimator, Discovery NM/CT 670 (GE Healthcare Japan Co, Tokyo, Japan). Two images were taken; one "early" at 30-40 minutes post-injection, and one "delayed" at 90-150 minutes. Characteristic SPECT-CT findings were identified according to timing, visibility, and extension of lymphatic enhancement in the lower abdominal, inguinal, genital, and pelvic regions.

Collected data included age, sex, body mass index (BMI), cancer etiology, treatment of cancer, symptomatic duration of lymphedema, ICG lymphography findings, and SPECT-CT findings. Prevalence of each SPECT-CT findings was compared between GL and control groups. Fischer exact probability test and Mann-Whitney *U* test were used for statistical analyses. Plus-minus values represented means ± standard deviations. *P*-value < 0.05 was set as statistical significance. This retrospective observational study was approved by the institutional review board. Written informed consent was waived by the review board, because only anonymous data was used.

RESULTS

Ten patients were included in this study. All were female (100%). Patient's age ranged from 43 to 85 years old (average 65.4 years), BMI from 19.6 to 43.0 kg/m^2 (average 24.7 kg/m^2). Etiology of secondary lymphedema included uterine cervical cancer in 5 (50%), uterine corpus cancer in 4 (40%), and pelvic lymphangioma resection and irradiation in 1 (10%). Eight (80%) patients received pelvic lymph node dissection, 2 (20%) patients pelvic lymph node biopsy, and 3 (30%) patients pelvic radiation therapy. Duration of symptom onset to presentation ranged from 1 to 305 months (average 100.8 months). Genital ICG lymphography stage included stage 0 in 3 (30%), stage I in 2 (20%), stage II in 3 (30%), stage III in 2 (20%) (*Table 2*).

Characteristic SPECT-CT findings included pauci-enhancement of inguinal lymph nodes (PEIL), genital dermal back flow (GDBF), non-enhancement of external iliac lymph nodes (NEEL), non-enhancement of common iliac lymph nodes (NECL) and non-enhancement of periaortic lymph nodes (NEPL). PEIL represents less than two (0 or 1) inguinal lymph nodes enhanced on either side, on delayed SPECT-CT (*Fig. 2*). GDBF represents evidence of dermal radioisotope accumulation in the genital areas (*Fig. 3*). NEEL, NECL and NEPL represents the complete absence of, respectively, the external iliac lymph nodes, common iliac lymph nodes, and para-aortic lymph nodes enhancement on delayed SPECT-CT (*Fig. 4*).

SPECT-CT showed PEIL in 7 (70.0%)

TABLE 2
Characteristics of Study Population

Sex	
Male	0 (0.0%)
Female	10 (100.0%)
Age*, years	65.4 (43-85)
BMI*, kg/m^2	24.7 (19.6-43.0)
Cancer etiology	
uterine cervical carcinoma	5 (50.0%)
uterine corpus carcinoma	4 (40.0%)
lower extremity angioma	1 (10.0%)
Cancer treatments	
pelvic lymph node dissection	8 (80%)
pelvic lymph node biopsy	2 (20.0%)
pelvic irradiation	3 (30.0%)
Lymphedema duration*, years	8.4 (0.1-25.4)
ICG lymphography	10 (100%)
Genital lymphedema	7 (70.0%)
Stage I	2 (20.0%)
Stage II	3 (30.0%)
Stage III	2 (20.0%)
Stage IV, V	0 (0.0%)
No-genital lymphedema (Stage 0)	3 (30%)

BMI, body mass index. Data are counts (percentages), otherwise indicated. * Data are averages (ranges).

cases, GDBF in 2 (20.0%) cases, NEEL in 2 (20.0%) cases, NECL in 5 (50.0%) cases, and NEPL in 4 (40.0%) cases. There was a statistically significant difference between GL group and control group in PEIL (100.0% vs. 0%, P = 0.002), whereas statistically significant difference was not detected in GDBF (12.5% vs. 33.3%, P = 0.490), NEEL (12.5% vs. 33.3%, P = 0.490), NECL (57.4% vs. 33.3%, P = 0.490), or NEPL (57.4% vs. 0%, P = 0.091) (*Fig. 5*).

DISCUSSION

The present study revealed characteristic SPECT-CT findings of secondary GL by comparing them to those of ICG lymphography. SPECT-CT finding of PEIL showed a statistically higher prevalence in patients with genital ICG lymphography stage I-V. Since ICG lymphography is an accurate diagnostic modality for detecting abnormal lymphatic circulation, these results are clinically relevant allowing accurate and early diagnosis of GL with SPECT-CT. To the best of our knowledge, this is the first study reporting characteristic SPECT-CT findings of GL based on definitive pathophysiological diagnosis based on ICG lymphography (20). Based on the study results, a clinician can

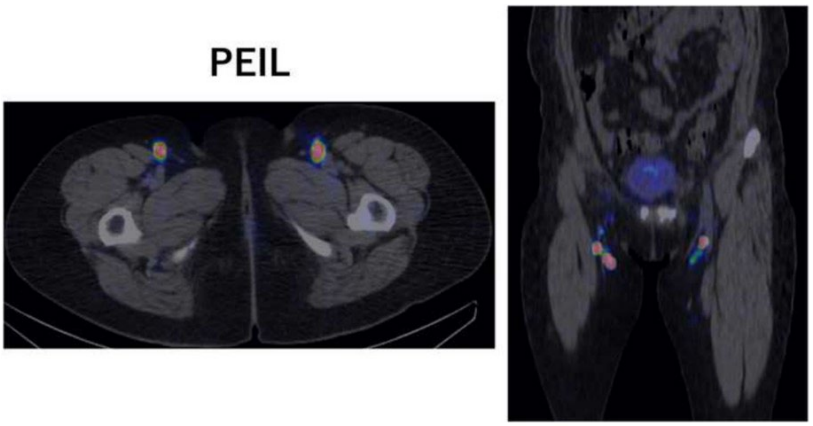

Fig. 2. *SPECT-CT images showing pauci-enhancement of inguinal lymph nodes (PEIL). Only one inguinal lymph node was enhanced in the left groin.*

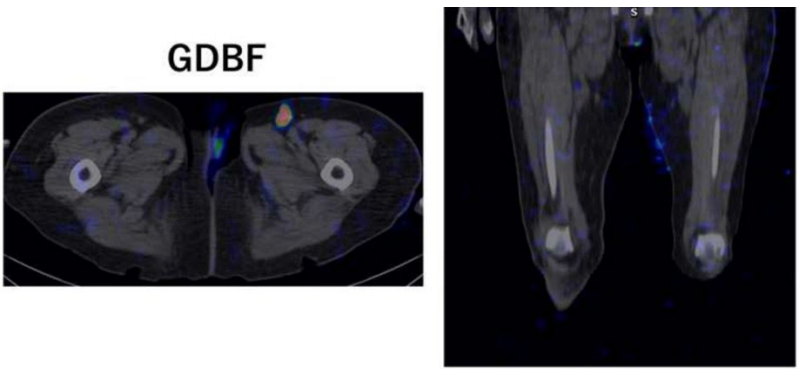

Fig. 3. *SPECT-CT images showing genital dermal back flow (GDBF). Dermal backflow was detected in the genital region.*

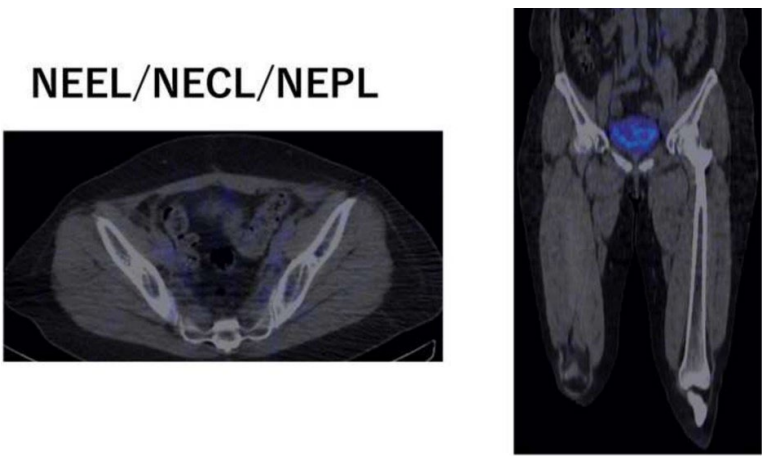

Fig. 4. *SPECT-CT images showing non-enhancement of external iliac lymph nodes (NEEL), non-enhancement of common iliac lymph nodes (NECL), and non-enhancement of periaortic lymph nodes (NEPL). The external iliac, common iliac, and para-aortic lymph nodes showed no enhancement on both sides.*

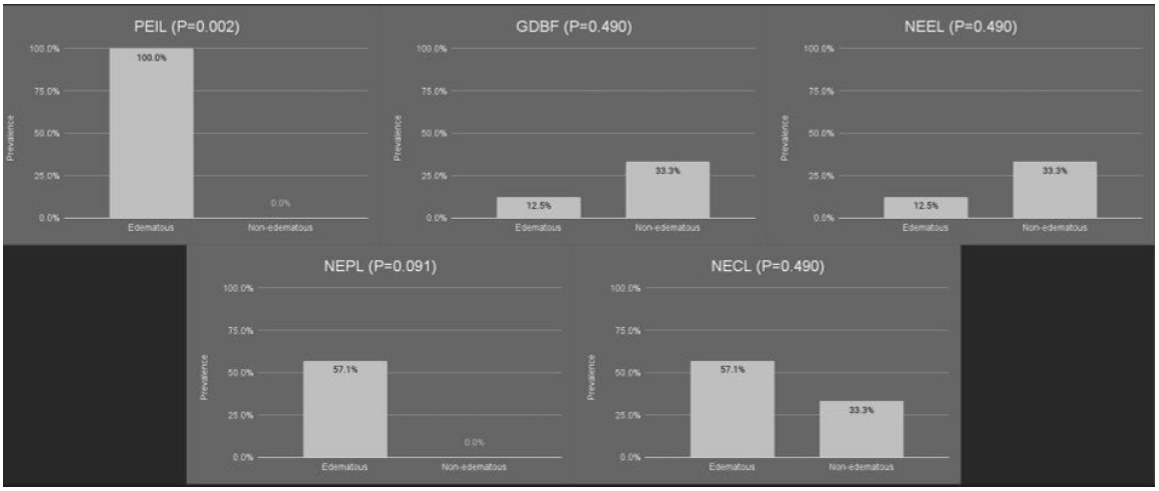

Fig. 5. *Prevalence comparison of characteristic SPECT-CT findings between GL group and control group. A statistically significant difference was observed in PEIL (100% vs. 0%, P = 0.002), whereas no significant difference was seen in GDBF (12.5% vs. 33.3%, P = 0.490), NEEL (12.5% vs. 33.3%, P = 0.490), NECL (57.4% vs. 33.3%, P = 0.490), or NEPL (57.4% vs. 0%, P = 0.091).*

suspect GL not to miss a chance of timely intervention, when delayed SPECT-CT image shows none or only one enhanced inguinal lymph node. This finding is considered to represent loss or significantly deterioration of inguinal lymph nodes' function. Anatomical knowledge that lymph in the genital-pubic areas is drained into the inguinal lymph nodes supports this finding.

This study did not show a statistically significant diagnostic finding of GL on SPECT-CT relating to the pelvic lymph nodes, of which certainly are the cause of secondary GL and LEL in the setting of pelvic lymph node dissection and/or irradiation. Previous studies have revealed the importance of the external iliac lymph nodes in the pathophysiology of LEL and GL (1,24,25). The seeming lack of diagnostic utility of external iliac lymph node enhancement is largely due to small sample size of the study. Another possible reason would be that functional inguinal lymph nodes compensate genital lymph drainage despite dysfunction of the external iliac and the pelvic lymph nodes (26-28). Only after the inguinal lymph nodes become dysfunctional, genital lymph drainage would be compromised, when SPECT-CT shows PEIL.

Since SPECT-CT uses the same principles as lymphoscintigraphy, which is the gold standard and most commonly used tool for lymphedema evaluation, SPECT-CT can be applied for GL evaluation in most lymphedema centers (7-10,14,18). Although additional SPECT scanning is required, a protocol for lymph flow visualization, such as injected isotope/volume/sites and time interval for scanning, is the same between lymphoscintigraphy and SPECT-CT. SPECT-CT is widely used for LEL evaluation, in which the genital region is also scanned. Therefore, GL evaluation is readily available with the use of images of SPECT-CT for LEL. As most cases of GL are associated with LEL and underestimated by both the patient and medical staff, appropriate evaluation of GL is critical for timely intervention. It would be of clinical significance to compare genital and whole-body lymph flows for evaluation of GL, although it is beyond the current study aim and was not conducted. Currently, SPECT-CT is not part of routine evaluation in lymphedema as articulated in published guidelines (24). When SPECT-CT is performed for LEL evaluation,

medical staff should also pay attention to the genital findings. As shown in Figure 4, tracer uptake in the bladder can be interpreted as dermal backflow in the genitalia on lymphoscintigraphy, application of SPECT-CT plays an important role in GL evaluation.

Limitations of the study included the small sample size, limited ethnicity and sex; only ten Japanese females were included in the study. Other limitations include the retrospective observational nature of the study, no comparison with interventions, and lack of long-term follow-up. With increased number of cases, SPECT-CT findings other than PEIL would show statistically significant differences in prevalence between patients with and without GL. Independent factors associated with GL should be clarified using multivariate analysis with larger study cohort. Since GL is a progressive disease, development of a severity grading scheme based on SPECT-CT is warranted for future study. Although further studies are needed to clarify the usefulness of SPECT-CT to improve management of GL, SPECT-CT has the potential to allow appropriate diagnosis and evaluation of secondary GL in patients with secondary LEL.

CONCLUSIONS

Characteristic SPECT-CT findings in secondary GL were revealed by comparison to genital ICG lymphography. SPECT-CT finding of PEIL can be used for diagnosis of GL.

CONFLICT OF INTEREST

All authors declare no financial conflict of interest regarding this manuscript.

REFERENCES

1. Todo, Y, R Yamamoto, S Minobe, et al: Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy. Gynecol. Oncol. 1 (2010), 60-64.
2. Tada, H, S Teramukai, M Fukushima, et al: Risk factors for lower limb lymphedema after lymph node dissection in patients with ovarian and uterine carcinoma. BMC Cancer 9 (2009), 47.
3. Yamamoto, T, I Koshima, H Yoshimatsu, et al: Simultaneous multi-site lymphaticovenular anastomoses for primary lower extremity and genital lymphoedema complicated with severe lymphorrhea. J. Plast. Reconstr. Aes. 64 (2011), 812-815.
4. Cheville, AL, CL McGarvey, JA Petrek, et al: Lymphedema management. Semin. Radiat. Oncol. 13 (2003), 290-301.
5. Whitaker, J: Best practice in managing scrotal lymphoedema. Br. J. Community Nurs. 12 (2007), S17-S18, 20-21.
6. McDougal, WS: Lymphedema of the external genitalia. JPN. J. Urol. 170 (2003), 711-716.
7. Cheng, MH, M Pappalardo, C Lin, et al: Validity of the novel Taiwan lymphoscintigraphy staging and correlation of Cheng lymphedema grading for unilateral extremity lymphedema. Ann. Surg. 268 (2018), 513-525.
8. Pappalardo, M, MH Cheng: Lymphoscintigraphy for the diagnosis of extremity lymphedema: Current controversies regarding protocol, interpretation, and clinical application. J. Surg. Oncol. 121 (2020), 37-47.
9. Pappalardo, M, C Lin, OA Ho, et al: Staging and clinical correlations of lymphoscintigraphy for unilateral gynecological cancer-related lymphedema. J. Surg. Oncol. 121 (2020), 422-434.
10. Akita, S, N Mitsukawa, T Kazama, et al: Comparison of lymphoscintigraphy and indocyanine green lymphography for the diagnosis of extremity lymphoedema. J. Plast. Reconstr. Aes. 66 (2013), 792-798.
11. Soga, S, F Onishi, A Mikoshi, et al: Lower limb lymphedema staging based on magnetic resonance lymphangiography. J. Vasc. Surg.-Venous L. 10 (2022), 445-453.
12. Cellina, M, G Oliva, A Menozzi, et al: Non-contrast magnetic resonance lymphangiography: an emerging technique for the study of lymphedema. Clin Imag. 53 (2019), 126-133.
13. Weiss, M, RGH Baumeister, A Frick, et al: Primary lymphedema of the lower limb: The clinical utility of single photon emission computed tomography/CT. Korean J. Radiol. 16 (2015), 188-195.

14. Hassanein, AH, RA Maclellan, FD Grant, et al: Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of false-negative tests. Plast. Reconstr. Surg. 5 (2017), e1396.
15. Rockson, SG: Advances in lymphedema. Circ. Res. 128 (2021), 2003-2016.
16. Yamamoto, T, N Yamamoto, H Yoshimatsu, et al: Factors associated with lymphosclerosis: An analysis on 962 lymphatic vessels. Plast. Reconstr. Surg. 140 (2017), 734-741.
17. Yamamoto, T: Onco-reconstructive supermicrosurgery. Eur. J. Surg. Oncol. 45 (2019), 1146-1151.
18. Yang, JCS, SC Wu, WC Lin, et al: Supermicrosurgical lymphaticovenous anastomosis as alternative treatment option for moderate-to-severe lower limb lymphedema. J. Am. Coll. Surgeons 230 (2020), 216-227.
19. Polomska, AK, ST Proulx: Imaging technology of the lymphatic system. Adv. Drug Deliver. Rev. 170 (2021), 294-311.
20. Hareyama, H, K Ito, K Hada, et al: Reduction/prevention of lower extremity lymphedema after pelvic and para-aortic lymphadenectomy for patients with gynecologic malignancies. Ann. Surg. Oncol. 19 (2012), 268-273.
21. Bats, AS, C Nos, C Bensaïd, et al: Lower-limb drainage mapping for lymphedema risk reduction after pelvic lymphadenectomy for endometrial cancer. Oncologist 18 (2013), 174-179.
22. Iimura, T, Y Fukushima, S Kumita, et al: Estimating lymphodynamic conditions and lymphovenous anastomosis efficacy using (99m) Tc-phytate lymphoscintigraphy with SPECT-CT in patients with lower-limb lymphedema. Plast. Reconstr. Surg. 3 (2015), e404.
23. Weiss, M, RG Baumeister, A Frick, et al: Primary lymphedema of the lower limb: The clinical utility of single photonemission computed tomography/CT. Korean J. Radiol. 16 (2015), 188-195.
24. O'Donnell Jr., TF, GM Allison, MD Iafrati: A systematic review of guidelines for lymphedema and the need for contemporary intersocietal guidelines for the management of lymphedema. J. Vasc. Surg.-Venous L. 8 (2020), 676-684.
25. 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 and Lym Dis 2013;1(4):400-405.
26. Yamamoto, T, N Yamamoto, M Furuya, et al: Genital lymphedema score: Genital lymphedema severity scoring system based on subjective symptoms. Ann. Plast. Surg. 77 (2016), 119-121.
27. Yamamoto, T, H Yoshimatsu, N Yamamoto: Complete lymph flow reconstruction: A free vascularized lymph node true perforator flap transfer with efferent lymphaticolymphatic anastomosis. J. Plast. Reconstr. Aes. 69 (2016), 1227-1233.
28. Yamamoto, T, N Yamamoto, M Yamashita, et al: Efferent lymphatic vessel anastomosis (ELVA): Supermicrosurgical efferent lymphatic vessel-to-venous anastomosis for the prophylac-tic treatment of subclinical lymphedema. Ann. Plast. Surg. 76 (2016), 424-427.

Takumi Yamamoto, MD, PhD
Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan
Toyama 1-21-1, Shinjuku-ku, Tokyo 162-8655, Tokyo, Japan
Phone: +81 3 3202 7181, Fax: +81 3 5800 6929.
E-mail: tyamamoto-tky@umin.ac.jp