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Suitable therapy options for sub-clinical and early-stage lymphoedema patients



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KEYWORDS

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Summary *Background:* The best therapeutic approach for patients with sub-clinical lymphoedema and symptomatic early-stage lymphoedema has not been determined yet.

Methods: The prognosis of lymphatic function after lymphadenectomy for gynaecological cancer was observed in a cohort study of 192 lower limbs. Lymphatic function was evaluated by indocyanine green lymphography. Splash patterns were examined to determine if patients with this pattern tended to progress to symptomatic lymphoedema, and the efficacy of the compression therapy was also investigated. We also investigated the efficacy of lymphaticovenular anastomosis (LVA) in patients who exhibited a stardust pattern.

Results: Patients with splash patterns on lymphography may progress to symptomatic lymphoedema with a significantly higher frequency compared with the others, with a relative ratio of 1.62. Compression therapy did not slow the progression of patients with splash patterns to stardust patterns. LVA for the patients who had recently shown stardust patterns eliminated the need for compression therapy in 44.8% of patients.

Conclusion: Patients with splash patterns should be followed up carefully for sub-clinical lymphoedema. However, there is no method to completely prevent these patients from developing stardust patterns associated with symptomatic lymphoedema. When patients become symptomatic, their lymphatic function may be improved by LVA. However, the limited effectiveness of this procedure should be clearly explained to patients before surgery.

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Secondary lymphoedema following lymph node dissection in patients with gynaecological cancer greatly affects their quality of life.¹ The importance of early diagnosis and therapy intervention for patients with lymphoedema has been reported.^{2–6} In most cases, lymphatic function has been compromised before symptoms develop.^{4,6} The concept of sub-clinical lymphoedema was proposed to represent patients with decreased lymphatic function but without clinical symptoms.^{2,4}

The best therapeutic approach for patients with sub-clinical lymphoedema and symptomatic early-stage lymphoedema has not been determined yet. Although the cornerstone of lymphoedema therapy is conservative, such as compression therapy, it is a lifelong burden for patients. The efficacy of compression therapy in preventing the progression of sub-clinical lymphoedema has not been proven.

When surgical therapy is planned for a patient with early-stage lymphoedema, the goal is to eliminate the need for continued compression therapy. There have been a few case reports in which supermicrosurgical therapy with lymphaticovenular anastomosis (LVA) allowed early-stage lymphoedema patients to discontinue compression therapy.^{4,5} However, no prospective controlled study has investigated the efficacy of surgery for early-stage lower limb lymphoedema.

Indocyanine green (ICG) lymphography is reported to be a useful tool to evaluate lymphatic function.^{3,6–10} ICG images are classified into either a normal linear pattern or three dermal backflow patterns (splash, stardust and diffuse) (Figure 1).^{6,9} The order of severity of these patterns increases from splash to diffuse.

We previously reported a cohort of patients who underwent lymph node dissection for gynaecological cancer and found that patients with splash patterns did not always develop symptomatic lower extremity lymphoedema,⁶ and that some of them improved to normal linear patterns without therapy. By contrast, most patients with stardust patterns developed symptomatic lymphoedema, and their lymphatic function never improved with conservative therapies. These observations led to the conclusion that splash patterns are indicative of reversible lymphatic disorder, and these patients should not be treated by surgical methods.

To establish a therapeutic approach for sub-clinical and early-stage lymphoedema, it is very important to

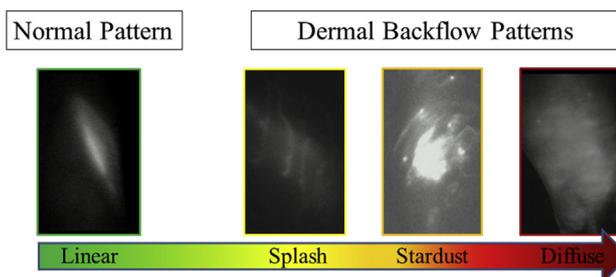


Figure 1 Indocyanine green lymphography findings are categorized into 4 patterns. Dermal backflow patterns generally progress from splash to stardust to diffuse as the severity of the lymphatic disorder increases.

understand what splash patterns mean clinically. The present study primarily aimed to investigate whether patients with splash patterns tend to progress to symptomatic lymphoedema more often compared with other patients. In other words, we investigated whether patients with splash patterns have sub-clinical lymphoedema. We also assessed the effect of compression therapy on their prognoses.

Because the majority of the patients with stardust patterns have symptomatic lymphoedema, there seems to be no doubt that compression therapy is necessary for these patients.^{3,6}

We investigated the efficacy of surgery for early-stage lower limb lymphoedema in patients who exhibited stardust patterns on ICG lymphography and were still considered clinical stage I as graded by the International Society of Lymphology (ISL) staging system.¹¹

Patients and methods

Among consecutive gynaecological cancer patients who underwent pelvic and/or para-aortic lymph node dissection at the Chiba University Hospital (Chiba, Japan) from August 2010 to July 2012, 192 lower limbs of 96 patients were included in the present cohort study. The trial protocol was approved by our institutional review board, and written informed consent was obtained from all subjects. Exclusion criteria included iodine allergy, pregnancy, recurrence after previous surgery or psychiatric disorders. Furthermore, we excluded patients who could not be followed up >12 months after surgery because they were unable to walk, had poor prognoses, underwent lymph node removal or decided to discontinue participation. Lymph node dissection procedures were standardised, and the retroperitoneum was left open at surgery to minimise the occurrence of lymphoedema.¹²

Lymphatic function was evaluated before lymphadenectomy after removal of the drainage tube 1–2 weeks, 1-month and 3 months after surgery, and every 3 months thereafter in all patients. Lymphatic function was assessed by ICG lymphography by injecting 0.3 ml subcutaneous ICG into the first web space of both lower limbs. One hour after injection, circumferential fluorescent images of lymphatic drainage channels were obtained using a Photodynamic Eye infrared camera system (Hamamatsu Photonics K.K., Hamamatsu, Japan).

The lymphoedematous volume of the limbs was calculated using the lower extremity lymphoedema (LEL) index, which was calculated from a 5-point circumference of the limb (superior edge of the patella, 10 cm above and below the patella, lateral malleolus and dorsum of the foot), and body mass index for quantitative assessment of lymphoedema severity.¹³

Before the patients became symptomatic and exhibited stardust pattern lymphoedema,^{3,6} some showed splash patterns (splash pattern group), while others did not (the non-splash pattern group). To determine whether splash patterns were indicative of sub-clinical lymphoedema, incidence rates of stardust patterns were compared between these two groups.

When a patient developed splash patterns, she received guidance about self-therapy techniques, such as skin care,

exercise, elevation and compression hosiery, as described in the Best Practice for the Management of Lymphoedema by Lymphoedema Framework.¹⁴ Although patients followed most of these therapies, compression hosiery is burdensome for patients to wear daily even though it is covered by insurance in Japan. Patients were allowed to choose if they wanted to receive compression therapy (compression therapy for the splash pattern group and the control group, correspondingly) after the therapy was explained to them. LEL index and ICG lymphography were evaluated every 3 months thereafter. Lymphatic function prognosis was compared between these two groups.

When patients showed stardust patterns, they received supervised conservative compression hosiery therapy for at least 3 months. Then, each patient was informed of the advantages and disadvantages of surgical and conservative therapy both orally and in writing, and the patients decided whether to continue with conservative or surgical therapy. In the surgical therapy group, supermicrosurgical LVA using subdermal venules through small skin incisions was performed because it was believed to be the least invasive method.^{15–19} Briefly, under local anaesthesia, incisions were made on the patient's thighs and lower legs above the ankle. Multiple side-to-end anastomoses were performed between the collecting lymphatics and similar-sized subdermal venules.^{16,20} Following surgery, the affected limb was wrapped loosely with compression bandages and kept elevated on a pillow. Patients were recommended to stay at the hospital for 7 days after surgery. All patients continued conservative therapies, including compression hosiery, beginning 3 weeks after surgery for 3 months after LVA, and their LEL index and lymphatic function were re-evaluated every 3 months. If lymphatic function improved to splash or linear patterns during follow-up, the patients were considered to have significantly improved and allowed to perform their routine activities without compression

hosiery. LEL index and lymphatic function were evaluated every 3 months in the conservative therapy group. The prognosis for lymphatic function was compared between these two groups. All patients were assessed by a single plastic surgeon.

Statistical analyses

A standard chi-squared test and Fisher's exact test were used to compare ICG lymphography findings between both the groups. A paired *t*-test was used to compare the improvement rates of the LEL index before and after therapies. Statistical analyses were performed using Statistical Package for Social Science (SPSS) software, version 20 (IBM SPSS, Inc., Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

Results

The mean age of the 96 women included in this study was 54.1 ± 11.4 years (mean \pm standard deviation (SD)). The mean value of body mass index before lymph node dissection was 22.0 ± 3.2 . The mean follow-up period was 20.9 ± 2.2 after lymph node dissection. Initially, normal linear patterns were observed in all 192 limbs. Except for temporal atypical changes during the immediate post-operative period, ICG lymphography findings during the natural course or with conservative therapies were categorised into six groups (Figure 1). In group 1, normal linear patterns persisted throughout the study. In group 2, splash patterns were observed once, but they subsequently improved to normal linear patterns. In group 3, splash patterns persisted throughout the study. In group 4, stardust patterns were observed after splash patterns. In group 5, splash patterns were not observed before stardust patterns; stardust patterns were observed after linear patterns and persisted throughout the study (until surgery). In group 6, only one limb was affected in which the stardust patterns had advanced to diffuse patterns. The number of limbs in each group and the mean durations of each finding are shown in Figure 2.

A total of 75 limbs that exhibited splash pattern in the study were included in group 2, 3 or 4. Overall, 27 of them (36%) advanced to stardust patterns. Most limbs ($n = 117$) were categorised into groups 1, 5 and 6 and were considered the non-splash pattern group. We found that 26 of them (22.2%) advanced to stardust patterns. A statistically significant correlation was observed in the frequency of developing stardust patterns between the splash pattern and non-splash pattern groups ($P = 0.037$). The relative risk of the splash pattern group advancing to the stardust pattern was 1.62 (Table 1).

Among the 75 limbs with splash patterns, 24 underwent compression therapy while 51 did not. In the compression therapy group, stardust patterns were later observed in seven limbs (29.1%). In this group, the mean duration from splash pattern onset to stardust pattern onset was 5.9 ± 6.0 months. In the control group, stardust patterns were later observed in 21 limbs (41.2%), and the mean duration from splash pattern onset to stardust pattern onset was 7.0 ± 10.0 months. There was no significant correlation

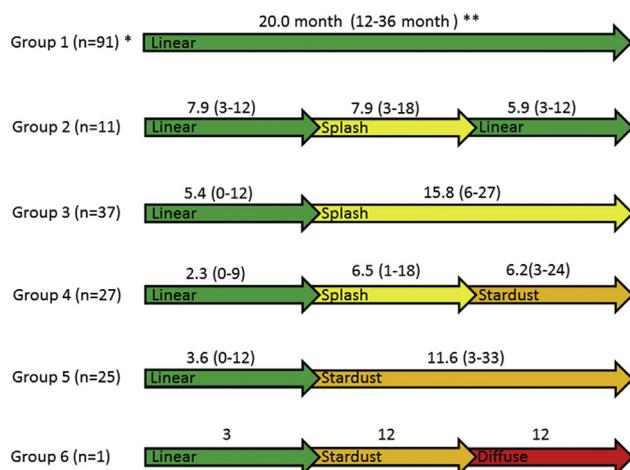


Figure 2 Transition of lymphatic function in 192 limbs during natural course or with conservative therapy. Lymphatic function was evaluated with Indocyanine green lymphography. Dermal backflow patterns generally progress from splash to stardust to diffuse as lymphatic disorder severity increases. * Number of limbs ** Mean duration \pm standard deviation (months).

Table 1 Correlation between the incidence of splash patterns and stardust patterns.

	Splash patterns (+)	Splash patterns (-)	Total
Stardust patterns (+)	27	26	53
Stardust patterns (-)	48	91	139
Total	75	117	192

Splash patterns (+): Splash patterns were observed during the study.

Splash patterns (-): Splash patterns were never seen.

Stardust patterns (+): Stardust patterns were observed during the study.

Stardust patterns (-): Stardust patterns were never seen.

between the two groups with respect to the rate of progression to stardust patterns ($P = 0.316$) (Table 2).

After the observation period for 53 limbs with stardust patterns was complete, 29 received surgical therapy. The mean time from lymph node dissection to surgery was 12.0 ± 4.9 months. The mean number of anastomoses for a limb was 4.36 ± 1.47 . The mean follow-up period after LVA was 12.1 ± 5.4 months. In this group, lymphatic function improved to normal linear patterns in three limbs and improved to splash patterns in 14 limbs. Stardust patterns persisted in 12 limbs; however, the area affected by stardust patterns did not extend in any of the patients who underwent LVA. Among 17 limbs that showed improved lymphatic function, 13 could discontinue compression therapy. The compression hosiery-wearing time was reduced in the other four patients; however, it had to be used on days when they were required to stand for extended periods. In total, 13 of 29 limbs (44.8%) in the surgical therapy group no longer required compression therapy. No surgery-related complications were observed. The mean number of anastomoses for a limb in which lymphatic function improved was 4.82 and that of the others was 4.42, which was not significantly different ($P = 0.413$ by two-sample *t*-test). Twenty-four limbs that showed stardust patterns did not receive surgical therapy

Table 2 Correlation between incidence of conservative therapy for patients with splash patterns and stardust patterns.

	Control	Compression	Total
Stardust patterns (+)	30	17	47
Stardust patterns (-)	21	7	28
Total	51	24	75

Control: Although patients underwent skin care, exercise/movement, and elevation, compression therapy was not performed.

Compression: Patients started to receive garment compression therapy with other conservative therapies.

Stardust patterns (+): Stardust patterns were observed later.

Stardust patterns (-): Stardust patterns were not observed during the study.

but underwent conservative therapies, such as compression. The mean follow-up duration after progression to stardust patterns in this group was 12.5 ± 7.7 months. In this group, none of the patients showed improvement in lymphatic function (change from stardust to splash or linear patterns). Lymphatic function became apparently worse in nine limbs; the range of stardust patterns extended distally and a limb showed further progression to diffuse patterns. Moreover, four of these nine limbs also advanced clinically to stage II according to the ISL staging system.^{5,6,12} According to the Best Practice for the Management of Lymphoedema,¹⁴ intensive therapies, including multilayer inelastic lymphoedema bandaging, are necessary to manage stage II patients. Therefore, these four patients started to receive intensive therapy. A statistically significant difference was observed regarding the frequency of improvement in early stardust patterns between the surgical and conservative therapy groups ($P < 0.001$) (Table 3).

With respect to lymphoedematous volume of the limbs, the LEL index of the limbs in the surgical therapy group was 253.8 ± 23.4 before lymph node dissection, 255.7 ± 22.7 just before LVA and 245.2 ± 19.0 after LVA and during follow-up. The LEL was significantly improved after LVA ($P < 0.001$). In the compression (control) group, the LEL was 252.8 ± 24.8 before lymph node dissection and 252.4 ± 23.7 after follow-up. Even in the control group, the LEL index was not significantly less during the study. However, when we assessed nine limbs with decreased lymphatic function in the control group, we found that the LEL index had significantly worsened from 249.0 ± 21.4 before lymphadenectomy to 262.7 ± 26.6 at the end of follow-up ($P = 0.033$).

Case report

Case 15

A 63-year-old female presented with lymphoedema localised to her left thigh. ICG lymphography revealed a stardust pattern. The patient developed symptomatic lymphoedema 3 months after lymph node dissection for ovarian cancer. After 5 months of conservative therapy with compression hosiery, stardust pattern persisted; thereafter, she

Table 3 Comparison of lymphatic function between conservative and surgical therapy for patients with early stardust patterns.

	Conservative therapy	Surgery	Total
Improved	0	17	17
Not improved	24	12	36
Total	24	29	53

Surgery: Multiple lymphaticovenular anastomosis were performed and compression therapy was performed for 3 months after surgery.

Conservative therapy: Patients received conservative therapies.

Improved: Lymphatic function was improved to splash or linear patterns after follow-up.

Not improved: Stardust or diffuse patterns were observed after follow-up.

underwent multiple LVA procedures of her left lower extremity, including five side-to-end anastomoses. Her post-operative ICG lymphography findings revealed improvement to the normal linear pattern. She was disease-free without undergoing compression therapy 3 months following LVA until the final follow-up 7 months later. The LEL index was 251.0 under compression therapy before LVA, and it improved to 242.8 at the final follow-up after LVA (Figure 3).

Discussion

Improvements following lymphoedema therapy can be evaluated on the basis of changes in limb size^{6,13,14,17}; however, for patients in the early phase of the lymphatic disorder, there is a prominent circadian variation in limb size, and the influence of compression therapy is extensive. Therefore, results should be evaluated objectively. One of the most remarkable advantages of ICG lymphography compared with lymphoscintigraphy for evaluating the lymphatic function is that early dysfunction can be detected as splash patterns.^{10,21} In the present study, we demonstrated for the first time that patients who showed splash patterns could develop stardust patterns and experience symptomatic lymphoedema at a significantly higher rate than those who did not. When a patient shows splash patterns on ICG, they must learn about appropriate therapy for lymphoedema, such as skin care, exercise/movement, elevation and compression hosiery. Here, compression hosiery did not significantly prevent or delay the onset of stardust patterns. However, currently, there is no ideal therapy to prevent worsening in patients who show splash patterns on ICG. The rate of conversion to stardust patterns was not significantly lower in the compression group than in the control group (29.1% vs. 41.2%, respectively). Furthermore, compression therapy is non-invasive, and we believe it should be used for patients with splash pattern after they receive an explanation of its limitations.

The lymphoedematous volumes in patients who had just progressed to stardust patterns and were in ISL stage I lymphoedema were not very large under adequate compression therapy. Therefore, although LVA in these patients could significantly thin down their extremity, the lymphoedematous volume was not high. However, it could improve lymphatic function in patients who were not helped by compression therapy. In the present study, when only compression therapy was continued, nine of 24 patients apparently worsened and no patient improved during the study period. By contrast, in the surgical therapy group, no patients experienced acute cellulitis or worsening of the lymphoedema status during follow-up; however, less than half (44.8%) the patients whose lymphatic function apparently improved no longer required compression therapy. Despite performing the same surgery on patients with the same stage, some patients became disease-free while others did not show much improvement. In the future, we plan to assess more patients and investigate differences between patients who do and do not require further compression therapy.

In our opinion, when stardust pattern is observed in a patient, LVA can be performed because it can prevent the

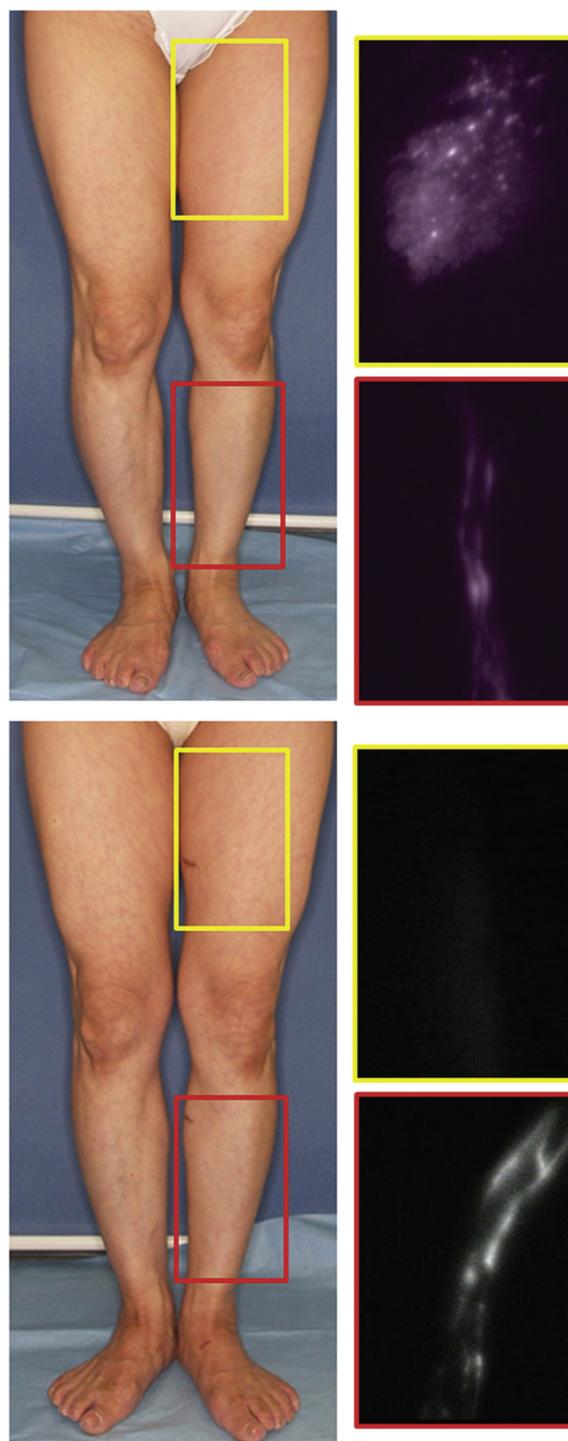


Figure 3 (above, left) A 63-year-old female presented with lymphedema localized to her left thigh. (above, right) Before surgery, ICG lymphography revealed stardust pattern on her left thigh (yellow frame) and a linear pattern on her left lower leg (red frame). (below, left) Ten months after surgery, she was free from compression therapy. (below, right) After surgery, the dermal backflow pattern vanished and a linear pattern was observed.

worsening of and may even improve the lymphatic function. However, all patients with lower extremity lymphoedema should be informed about the limitations of LVA in advance. In the present study, even in the earliest stages of symptomatic disease, more than half of patients had to continue compression therapy after LVA.

Conclusion

Patients with splash patterns on ICG lymphography are more likely to develop symptomatic lymphoedema than patients without this pattern, with a relative ratio of 1.62. There are no proven methods that prevent stardust patterns or symptomatic lymphoedema. When patients become symptomatic with stardust pattern lymphoedema, their lymphatic function may be improved by LVA. However, the efficacy of LVA was not stable in the present study, and patients should always be informed about the limitation of the surgery in advance.

Ethical consent

This study was carried out in Chiba University Hospital (Chiba, Japan) with the approval of the institutional review board and permission from the ethics committee. Written permission for the publication of photographs was obtained from all patients.

Conflict of interest/funding

None.

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