

Lower Leg Lymphedema in Patients with Gynecologic Cancer

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Cervical, endometrial, and ovarian cancers are treated with surgery, radiation, or chemotherapy, depending on the treatment strategy. Gynecologic surgeons traditionally perform hysterectomy and pelvic lymphadenectomy with or without paraaortic lymphadenectomy in cervical, endometrial, and ovarian cancer. Lymphedema results from excess lymphatic fluid in the lymphatic system and interstitial space with diminished transport capacity. The main components of lymphatic fluid are interstitial water and solid filtrate, which only drain into the lymphatic system, not the arteriovenous capillary system. Primary lymphedema develops without a definitive cause, whereas, secondary lymphedema results from exogenous causes such as surgery, radiation, infection, and cancer metastasis. Based on the CTCAE v4.0, the degree of lymphedema was divided into three categories. Risk factors for lower leg lymphedema (LLL) in gynecologic cancer have included vulva cancer, radiotherapy, high number of lymph nodes dissected and BMI. In this paper, pathophysiology and risk factors for LLL in gynecologic cancer was evaluated based on the previous literature review. More interventional trials are necessary to decrease the development of LLL in gynecologic cancer.

Key Words: Lymphedema • Gynecologic cancer • Surgery • Radiation • Chemotherapy

INTRODUCTION

Cervical, endometrial, and ovarian cancers are treated with surgery, radiation, or chemotherapy, depending on the treatment strategy [1-3]. Gynecologic surgeons traditionally perform hysterectomy and pelvic lymphadenectomy with or without paraaortic lymphadenectomy

in cervical, endometrial, and ovarian cancer [4]. Post-operative adjuvant radiotherapy is recommended for cervical cancer patients with high-risk factors such as parametrial invasion, lymph node metastasis, and involvement of the surgical margin in the pathology specimen, and may also be considered for cervical cancer patients with intermediate-risk factors such as deep stromal invasion, involvement of the lymphovascular space, and large tumor size [2].

Lower leg lymphedema (LLL) can develop after gynecological cancer treatment such as lymphadenectomy and/or radiotherapy [3,5-7]. The reported incidence of LLL in gynecologic cancer patients ranges from 1.0% to 50% [8,9]. Therefore, patients with LLL have a high likelihood of living with impaired quality of life, and can experience secondary complications such as lymph-

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angitis and fever, which may have adverse psychological and physical effects.

The goal of this review is to provide fundamental and clinical knowledge about LLL including pathophysiology, symptoms, diagnosis, risk factors, and management in gynecologic cancer patients.

MAIN

1. Pathophysiology of lymphedema

Lymphedema results from excess lymphatic fluid in the lymphatic system and interstitial space with diminished transport capacity. The main components of lymphatic fluid are interstitial water and solid filtrate, which only drain into the lymphatic system, not the arterio-venous capillary system. Solid components include protein, fatty acids, and leukocytes [10]. Lymphedema is divided into 2 types according to its etiology. Primary lymphedema develops without a definitive cause, whereas, secondary lymphedema results from exogenous causes such as surgery, radiation, infection, and cancer metastasis [11]. Lymphadenectomy destroys or obliterates the lymphatic systems, and radiation induces fibrosis of the lymphatic system with reduction of transport capacity. The combination of surgery and radiation can worsen decreased lymphatic system function [12,13]. Comorbid factors such as diabetes, hypoproteinemia, and vascular insufficiency can also exacerbate lymphedema [13].

LLL is often observed after lymphadenectomy or radiation for cervical cancer, because the lower extremity does not have additional capacity for collateral lymphatic drainage [11]. The protein filtrate in the congested lymphatic system induces aggregation of neutrophils and macrophages, and promotes fibrosis via tissue inflammation and accumulation of collagen fiber. Fibrosis and infection lead to dysfunction of lymph collectors and induce stasis of lymphatic flow. Finally, metaplasia and hyperkeratinization develop in overlying skin and are used as indicators of the severity of lymphedema [11]. Women with LLL can experience pain, swelling, walking difficulty, fever, skin defects, and lymphangitis.

2. Anatomy of the lymphatic system in the lower leg

The lymphatic vessels in the lower extremity are categorized into 2 groups: the superficial epifascial and deep subfascial lymphatic vessels. Lymph, which is mainly composed of water and protein, is transported by the epifascial lymphatic system from the skin and subcutaneous tissue, and the deep subfascial system drains lymph from bone and muscle [14]. The epifascial lymphatic system primarily drains into the superficial inguinal lymph nodes and the deep subfascial lymphatic vessels primarily drain into the deep inguinal lymph nodes. The inguinal lymph node groups then primarily drain into the external iliac lymph nodes in the pelvis. The distal iliac lymph nodes are located in the distal group of external iliac nodes and are the first to receive drainage from the inguinal lymph nodes. The external lymph node group receives lymph from the uterus and vagina and reportedly is a frequent site of metastasis in gynecologic cancer patients.

3. Diagnosis and evaluation of LLL

Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) have been widely used to evaluate the grades of lymphedema since 2009, and was primarily developed to evaluate treatment-related complications or toxicity in cancer patients (Table 1). Based on the CTCAE v4.0, the degree of lymphedema was divided into three categories: grade 1 shows trace thickening or faint discoloration; grade 2 shows marked discoloration, papillary formation, and impaired instrumental activity of daily living; and grade 3 is characterized by severe symptoms and limitations of self-care activity of daily living. CTCAE v4.0 makes a clear distinction between grades 2 and 3 in terms of limitation of daily activity, and does not use volume-based measurement. Hence, it can correct for measurement errors, which can be affected by anatomical variation or baseline differences among lymphedema patients.

Table 1. Common Terminology Criteria for Adverse Events (CTCAE)

Adverse effect		Grade	
Lymphedema	1	2	3
Description	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental activities of daily living	Severe symptoms; limiting self care activities of daily living

4. Symptoms of LLL

LLL usually develops within the first year after surgery for gynecologic cancer [9,15]. It can be asymptomatic or can induce distinct swelling, causing discomfort in daily life, with pain, stiffness, limitation of movement, a hot sensation, numbness, fatigue, sexual difficulty, and anxiety. These symptoms can deteriorate the quality of life [16]. LLL should be differentiated from other causes of a swollen leg, such as deep vein thrombosis, cellulitis, congestive cardiac disease, hypoalbuminemia, and renal disease [16].

5. Diagnosis of LLL

The diagnosis of LLL is usually apparent in cervical cancer patients with symptoms such as swelling, a sense of heaviness, pain, and a pulling sensation, and is confirmed on physical examination by a gynecologic oncologist, rehabilitation doctor, or lymphedema clinician. Computed tomography (CT) or magnetic resonance imaging (MRI) is performed to exclude recurrence of tumor in the pelvic cavity and Doppler ultrasonography is used to detect deep vein thrombosis in the lower leg [8].

Lymphoscintigraphy is noninvasive and can be used for further evaluations of LLL [17]. Radiopharmaceutical particle signals can be detected in soft tissue with lymphedema. Radionuclide tracer is injected into the subcutaneous layer in the web space between the first and second toes. Massage of the injection sites can help move the tracer through the lymphatic channels. After one hour, whole-body imaging is performed [17]. In lymphoscintigraphy, the radiotracer signal is not normally seen in the soft tissue. The tracer signal can be detected at the injection site and groin lymph nodes, but is usually weaker than that in lymphedema. In lymphedema, distinct accumulation of radioactive signals can be observed in soft tissue or lymphatic webs [18].

6. Risk factors for LLL

Inguinofemoral lymphadenectomy is part of the standard treatment for early-stage vulvar cancer [19], but frequently results in postoperative complications such as lymphedema, lymphocyst formation, wound infection, and cellulitis [7]. LLL more commonly develops in women who undergo lymphadenectomy than in those who only undergo lymph node sampling [5]. It is more frequently observed in patients who undergo

groin dissection than in those who undergo pelvic lymphadenectomy (70% vs. 40%). Hence, groin lymphadenectomy is a major risk factor for LLL, and the number of lymph nodes removed influences the development of LLL [15]. LLL is more frequently observed after treatment of vulvar cancer than after treatment of all other cancers [5]. Up to 47% of vulvar cancer patients subsequently develop LLL, whereas 18% of cervical and uterine cancer patients and 7% of ovarian cancer patients develop LLL after treatment [5].

In terms of treatment modality, radiotherapy was reported to be a high risk factor, but chemotherapy did not influence the development of LLL [5]. In addition, radiotherapy following removal of lymph nodes in the groin further increased the incidence of LLL [5]. Radiation-induced fibrotic scarring prevents restoration of the lymphatic duct.

Body mass index (BMI) is associated with increased risk for LLL in endometrial cancer [6]. However, Achouri et al. reported that development of LLL was not significantly affected by age, BMI, type of surgery (laparoscopy or laparotomy), the number of lymph nodes removed, or the presence of metastatic lymph nodes. They found that removal of lymph nodes under the iliac veins could prevent lymphatic drainage from both the lower leg and pelvic organs and induce LLL. In contrast, the use of postoperative drainage had a protective effect against the occurrence of LLL [9].

Inguinal lymph node removal during lymphadenectomy reportedly greatly increases the risk for development of lymphedema in vulvar cancer patients [20]. The distal external iliac lymph nodes are the first to receive lymphatic fluid from the inguinal node group draining most of the lower extremity [21]. Thus, excision of the distal external iliac lymph nodes during pelvic lymphadenectomy is presumed to be a probable risk factor for lymphedema in gynecologic cancer patients. Incidence and risk factors of LLL after treatment of cancer were summarized in Table 2 [3,5-8,22-32].

7. Efforts to reduce the development of LLL

Sentinel node dissection is currently performed for patients with cervical, endometrial, and vulvar cancer to reduce the incidence of LLL [16]. A sentinel lymph node is the first draining lymph node in a chain of other non-sentinel lymph nodes. Negative biopsy results for a sentinel lymph node may confirm the absence of metastasis to other non-sentinel lymph nodes [33]. A negative result for sentinel lymph node biopsy in pati-

Table 2. Incidence and risk factors of lower leg lymphedema (LLL) after treatment of cancer

Site of cancer	Author	Stage of cancer	Number of participants	Treatments	Key findings	Year
Cervix	Kim [8]	Ia-IIa	671	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL: 12.5% Adjuvant radiotherapy significantly increased the development of LLL	2012
Cervix	Fuller [22]	Ia-IV	173	Surgery including lymphadenectomy, with or without radiotherapy, or chemotherapy	Incidence of LLL: 23.4% Risk factor for LLL in cervix cancer includes laparoscopic radical hysterectomy, higher number of lymph nodes dissected, and FIGO stage	2008
Cervix	Bergmark [23]	Ib-IIa	332	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL in: 25.0%	2006
Cervix	Snijders-Keilholz [24]	Ia-IIa	233	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL: 10.9% Lymphadenectomy is a potent risk factor for LLL. There was no significant difference of the incidence of LLL between surgery only and surgery combined radiotherapy group	1999
Cervix	Chatani [25]	Ib-IIb	202	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL (10 year-follow up): 49.0% There was no significant difference of the incidence of LLL between surgery only and surgery combined radiotherapy group	1998
Endometrium	Ghezzi [27]	I-IV	261	Surgery including lymphadenectomy	Incidence of LLL: 13.0% There was no significant difference of the incidence of LLL between laparoscopy vs laparotomy group	2012
Endometrium	Todo [26]	I-IV	286	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL: 37.8% Risk factors for LLL in endometrial cancer include adjuvant radiation therapy, higher number of lymph nodes dissected, and removal of circumflex iliac nodes to the distal external iliac nodes	2010
Ovary	Lim [28]	Ia-IIc	71	Surgery including lymphadenectomy	Incidence of LLL in: 40.8% LLL in early stage ovary cancer was investigated	2014
Ovary	Matsuo [29]	I-IV	276	Surgery including lymphadenectomy	Incidence of LLL in ovary cancer: 6.5% LLL in ovary cancer is significantly associated with shorter survival	2011
Uterine corpus	Abu-Rustum [3]	Not demonstrated	1,289	Hysterectomy with or without lymphadenectomy	Incidence of LLL in: 5.06% Removal of 10 or more lymph nodes is a risk factor for LLL in uterine corpus cancer	2006
Vulva	Hinten [7]	Ib-IVb	164	Surgery including inguinofemoral lymphadenectomy	Younger age is an independent risk factor for LLL	2011
Vulva	Sawan [30]	Ib and above	14	Surgery including inguinofemoral lymphadenectomy, with/or without adjuvant radiotherapy	Incidence of LLL: 44.4% Feasibility study of use of graduated compression stockings to prevent LLL	2009
Cervix Endometrium	Mendivil [31]	I-II (cervix) I-IV (endometrium)	30 (cervix) 165 (endometrium)	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL: 3.6% Obesity is a risk factor for LLL. This study showed lower incidence of LLL compared to other studies Laparotomy induced higher incidence of LLL than laparoscopy	2016
Cervix Endometrium Ovary	Tada [32]	I-IV	258 (cervix) 301 (endometrium) 135 (ovary)	Surgery including lymphadenectomy, with or without radiotherapy	Incidence of LLL: 29.8% (cervix), 27.8% (endometrium), 21.1% (ovary) Ovarian cancer showed lower incidence of LLL than uterine and cervix cancer	2009
Cervix, Uterus, Ovary, Vulva	Beesley [6]	Not demonstrated	197 (cervix) 243 (uterus) 234 (ovary) 53 (vulva) 75 (other)	Surgery Radiotherapy	Vulva cancer showed highest incidence of LLL (36%) among gynecologic cancer Lymphadenectomy combined with radiotherapy is a risk factor for LLL in cervical cancer Lymphadenectomy combined with obesity is a risk factor for LLL in uterine and ovary cancer	2007
Cervix, Uterus, Ovary, Vulva	Ryan [5]	Not demonstrated	120 (cervix) 141 (endometrium) 141 (ovary) 68 (vulva) 17 (other)	Surgery including lymphadenectomy, with or without radiotherapy, or chemotherapy	Incidence of LLL: 18.3% 84% of LLL developed within the first 12 months after treatment Radiotherapy and surgery increased the development of LLL	2003

ents with vulvar cancer was closely correlated with low recurrence rates in the groin area according to the Groiningen International Study on Sentinel Nodes in Vulvar Cancer I (GROINSS-V I). A negative result was also associated with an increased survival rate and minimal complications [34]. Vulvar cancer patients were managed with intradermal injection of ^{99m}Tc -labeled sulfur colloid and isosulfan blue dye into the vulvar tumor, followed by lymphoscintigraphy during surgery. The ^{99m}Tc -labeled sulfur colloid was detected in the tumor and the blue dye provided a visible aid to the surgeon. Thus, sentinel node dissection potentially offered a less invasive alternative to conventional inguinofemoral lymphadenectomy [35].

Abu-Rustum et al. suggested omitting removal of the distal external iliac lymph nodes when there is little possibility of metastasis, to avoid the occurrence of postoperative LLL [36]. Moreover, the metastatic rate to distal external iliac lymph nodes is only 8% when other lymph node groups show metastatic lesions [37]. In addition, the most common sites for cervical cancer metastasis appear to be in the external iliac, obturator, and common iliac nodes, in that order [38]. According to previous data on sentinel lymph node mapping, the distal external iliac nodes do not involve the sentinel nodes in cervical cancer patients. Hareyama et al. [39] reported that preserving the distal external iliac lymph nodes during lymphadenectomy significantly decreased the incidence of LLL in patients with gynecologic cancer.

Wound drainage has frequently been used after inguinofemoral lymphadenectomy to reduce the occurrence of lymphedema or wound infection. Unfortunately, a standard protocol has not been published for the management and duration of drainage. Gould and Gaarenstroom et al. reported that they removed the wound drain when fluid production was less than 30-50 mL per day after at least 5 days [20]. The duration of wound drainage was not believed to influence the occurrence of complications [40].

8. Treatment

Treatments for LLL are divided into 3 categories: rehabilitation, surgery, and pharmacologic therapy [41]. Until now, complete decongestive therapy (CDT) has been recognized as the standard for limb lymphedema [42]. CDT includes manual lymph drainage, multilayer limb bandaging, enhancement of lymphatic pumping, scrupulous skin care, and use of compression garments [42]. Although CDT contributes to the reduction of LLL, the

individual role of each component is still not clear. Studies report that CDT can induce remarkable reduction after the first 5 days of treatment, but maintenance treatment is required for the improvement of lymphedema. Manual lymph drainage following compression therapy can contribute to the improvement of quality of life and symptoms.

Boris et al. reported 69% volume reduction of lymphedema using complex therapy in one affected lower leg [43]. Lymphedema reduction averaged 67.7% in the lower extremity using complete decongestive physiotherapy. Moreover, this reduction was continuously maintained in 86% of compliant patients for 9 months. The incidence rate of infection in the affected limb decreased to 0.65 per patient per year after decongestive therapy [44].

Manual lymphatic drainage has been regarded as effective for the treatment of lymphedema. However, it has limited application for all patients with LLL. To address this problem, intermittent pneumatic compression (IPC) was developed to replace manual lymphatic drainage. IPC is supported by lymphedema therapists and provides easy and inexpensive compression therapy. Zaleska et al. [41] reported that IPC can permanently express lymphatic fluid from edematous tissue with obliterated lymphatics into normal lymphatics. They found that the highest flow of 20 to 120 mL/1 hour cycle could be produced under compression pressure with 6 minutes of inflation on the affected limb. The pneumatic compression device is composed of multiple chambers that can inflate sequentially and generate differential gradient pressures. Thus, the device pushes lymphatic flow from a distal to proximal area and can prevent back-flow in the lymphatic vessels.

Zaleska et al. also observed significant and long-lasting reduction of limb circumference and improved tissue elasticity in the calf above the ankle without development of complications. The results imply that reduction of fluid pressure in tissue can prevent secondary changes such as fibrosis in the affected limb. Hence, they maintained that LLL can be managed with long-term IPC, using high pressure and prolonged inflation time [41]. This technique has been used effectively to diminish the volume of lymphedematous limbs. Moreover, it can be performed at home by lymphedema patients. However, there is no universal consensus on the appropriate frequency or other therapeutic parameters for IPC [45]. Patients with LLL should receive dietary modification, loose bandaging, and manual drainage of lymphatic flow [9].

Recently, Chang et al. [46] performed lymphovenous

bypass surgery for the treatment of LLL secondary to cancer treatment. Indocyanine green lymphangiography was used for the accurate identification of functional lymphatic vessels, and objective assessment of LLL severity. Moreover, it helped surgeons to find precisely an ideal incision site for the bypass surgery. Surgeons connected subdermal lymphatic vessels with adjacent venules less than 0.8 mm in diameter and drained overloaded fluid of lymphedematous tissue into the venous circulation for the increased transportation of lymph material [46]. 57% of the patients given bypass surgery showed improvement of LLL symptom. So, the authors insisted that lymphovenous bypass might be more useful for the treatment of upper extremity lymphedema than for the cure of LLL. Nguyen et al. [47] suggested that laparoscopic free omental lymphatic flap is very effective for the treatment of LLL. Because this technique mobilizes the flap pedicle containing gastric lymph node, it can increase the drainage of stagnant lymphatic fluid.

The destruction of tissue injuries arising from lymphedema was not clearly explained by a stasis of lymphatic flow alone [48]. Also, lymphedema was reported to be closely associated with inflammation condition. Hence, anti-inflammatory treatment was performed to cure the lymphedema in mouse model. Additionally, vascular endothelial growth factor C (VEGF-C) was regarded as a promising candidate for the treatment of lymphedema [49].

CONCLUSION

In this paper, pathophysiology and risk factors for LLL in gynecologic cancer was evaluated based on the previous literature review. More interventional trials are necessary to decrease the development of LLL in gynecologic cancer.

Conflicts of Interest

All authors declare no conflicts of interest.

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