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ABSTRACT

Lower extremity lymphedema is a chronic, often irreversible condition that affects many patients treated for gynecologic malignancies, with published rates as high as 70% in select populations. It has consistently been shown to affect multiple quality of life metrics. This review focuses on the pathophysiology, incidence, trends, and risk factors associated with lower extremity lymphedema secondary to the treatment of cervical, endometrial, ovarian, and vulvar cancers in the era of sentinel lymph node mapping. We review traditional and contemporary approaches to diagnosis and staging, and discuss new technologies and imaging modalities. Finally, we review the data-based treatment of lower extremity lymphedema and discuss experimental treatments currently being developed. This review highlights the need for more prospective studies and objective metrics, so that we may better evaluate and serve these patients.

radiation therapy and chemotherapy also contribute to the risk.¹ Though dangerous side effects are rare, the psychosocial consequences of lymphedema can be debilitating. Ryan et al showed that, among patients with lower extremity lymphedema, 27% reported a financial burden secondary to the diagnosis and 51% reported alterations in their daily activities.⁵ The derangement in esthetics and functioning that accompany this condition can lead to depression, anxiety, and a negative body image. In its severe stages, lymphedema can affect a patient's ability to perform the functions of daily living.⁶

Pathophysiology

In lymphedema, the buildup of stagnant, protein-rich extracellular fluid impairs normal oxygen and nutrient transport to tissues.¹ The change in hydrostatic pressure in the interstitium also results in cell death and

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Lymphedema is a chronic, complex process that affects approximately 20 million people worldwide, causing significant discomfort, morbidity, and financial burden for those affected. Lymphedema is defined as the accumulation of interstitial fluid, leading to soft tissue swelling, chronic inflammation, reactive tissue fibrosis, and abnormal adipose deposition.¹ There are two types of lymphedema: primary and secondary. Primary lymphedema is mostly due to an innate defect in the lymphatic system involving either the channels, nodes, or both, leading to aplasia, hypoplasia, or hyperplasia of these structures.^{1,2} Primary lymphedema is rare, typically occurring early in life, and is further classified based on the age of onset.¹ Secondary lymphedema is much more common and occurs when the lymphatics are damaged by underlying medical conditions such as cancer, obesity, surgery, trauma, infection, radiation, and other therapies.^{1,3} Secondary lymphedema is the focus of this review.

The most common cause of secondary lymphedema worldwide is infection. In the United States, however, malignancy and cancer-directed treatments account for the majority of cases.⁴ The incidence and prevalence of lymphedema after cancer treatments varies based on the surgical procedures performed and the use of additional therapies.³ The most common surgical cause is regional lymphadenectomy, and

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DIAGNOSIS AND ASSESSMENT

The diagnosis of lymphedema can be difficult, especially in its early stages. This has resulted in under-diagnosis even in the research setting. Early and accurate diagnosis of lymphedema is key to proper intervention and prevention of the irreversible sequelae of later-stage disease.

Please answer the following questions:

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Secondary lymphedema is due to:

- a. Hypoplastic lymphatic channels
- b. An innate defect in the lymphatic system
- c. Young age
- d. Damage by underlying medical conditions
- e. Abnormal adipose deposition

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Obesity is the most common cause of secondary lymphedema worldwide.

- a. True
- b. False

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Early and accurate diagnosis of lymphedema is key because:

- It enables proper intervention
- It may prevent the sequelae of later-stage disease
- Its pathophysiology and management are different to other causes of peripheral edema
- It is reversible
- All of the above

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Box 1 Disease states that can mimic lymphedema

Other disease states

- Morbid obesity
- Chronic venous insufficiency
- Cardiac/renal failure
- Hypoalbuminemia
- Complex regional pain syndrome Type 1
- Infection
- Musculoskeletal injury
- Myedema
- May–Thurner syndrome
- Obstructive sleep apnea
- Medication-induced peripheral edema
- Lipedema

It is critical to differentiate true lymphedema from other conditions that lead to swelling of the extremities and are often confused as lymphedema, because the pathophysiology, management, and reversibility are quite different. Other causes of peripheral edema which can mimic lymphedema (summarized in [Box 1](#)) include chronic venous insufficiency, cardiac/renal failure, hypoalbuminemia, and lipedema. It is important to note that some of these comorbid conditions are also risk factors for lymphedema and may occur concomitantly, further muddying the clinical picture.

History and physical examination play a large role in the diagnosis of lymphedema, however, other metrics should also be used in the diagnosis, grading, and measurement of treatment response ([Table 1](#)). Limb volume has long been utilized as a metric for measuring lymphedema as a quantitative adjunct to swelling noted by the patient or on physical examination.¹⁰ These measurements rely on a normal limb as an internal standard, or baseline measurements for comparison.¹⁰ The gold standard for volumetric measurement of lymphedema is the use of a water volumeter, which simply measures the true volume of a limb using displacement of water in a standardized container. This method has been shown to detect changes in volumes of <1%, however, it does not provide insight into the distribution of edema.¹¹ Though simple and easily reproducible, the method is inconvenient for patients, and it may be cumbersome to use in a clinical setting, especially with respect to

Limb circumference as measured by a non-elastic tape measure has also been used as a surrogate for differential limbs' volumes. These measurements can be taken at specified anatomical landmarks or at regular intervals along the length of the limb.¹² Though cut-offs may vary by method, a difference of 2 cm between limbs is considered diagnostic of lymphedema.^{13 14} This method is inexpensive and easily taught, which makes it attractive. However, the measurements are often not sensitive enough to detect small changes: furthermore they require a normal contralateral limb, which may not be possible in the setting of bilateral disease.¹² Mathematical formulae have also been used to correlate a series of standard tape measurement to volumes. The most commonly used is the Frustum Formula, which calculates volume by assuming that limbs are similar to cones. These methods attempt to maximize the simplicity of tape measurements and the utility of comparing volumes: they are not sets of linear measurements.¹⁵

A perometer is a more complex tool that utilizes parallel light-emitting diodes to measure corresponding extremity diameter throughout the length of the limb, allowing for volumetric assessment without using water displacement. Perometry has demonstrated higher interobserver reliability compared with tape measurements, especially for clinicians who do not regularly do such assessments.¹⁴ However, the high cost of this diagnostic tool prohibits its widespread use, especially in a clinical setting where many of these assessments are done.¹⁰

Other diagnostic modalities that examine intrinsic tissue changes include bioimpedance spectroscopy and tissue tonometry. Bioimpedance spectroscopy exploits the fact that edematous tissues have higher water content and a lower tissue resistance. Differential measurement of this resistance allows for an estimation of extracellular water volume as a surrogate marker for lymphedema.¹⁶ Bioimpedance spectroscopy enables the detection of subclinical lymphedema and may facilitate interventions to reduce the likelihood of the disease entering the irreversible stages. Importantly, bioimpedance spectroscopy technology does not require an internal control. This is relevant in the setting of gynecologic malignancy, where bilateral disease is more common.⁴ Tissue tonometry objectively measures the resistance of soft tissue to compression, thus acting as a surrogate for edema and tissue fibrosis changes in lymphedema. However, this technology also requires an internal

Which of the following statements regarding lymphedema diagnosis is false:

- a. Limb volume measured by water volumeter is the gold standard but is inconvenient for patients
- b. A difference of 2cm in limb circumference between limbs is diagnostic of lymphedema
- c. The Frustrum formula calculates volume by assuming that limbs are similar to cones
- d. A perometer uses light emitting diodes in series to measure extremity diameter throughout the length of the limb and has high interobserver variability
- e. Other diagnostic modalities include bioimpedance spectroscopy and tissue tonometry

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History and physical examination play a large role in the diagnosis of lymphedema, however, other metrics should also be used in the diagnosis, grading, and measurement of treatment response ([Table 1](#)). Limb volume has long been utilized as a metric for measuring lymphedema as a quantitative adjunct to swelling noted by the patient or on physical examination.¹⁰ These measurements rely on a normal limb as an internal standard, or baseline measurements for comparison.¹⁰ The gold standard for volumetric measure-

ment of lymphedema is the use of a water volumeter, which simply measures the true volume of a limb using displacement of water in a standardized container. This method has been shown to detect changes in volumes of <1%, however, it does not provide insight into the distribution of edema.¹¹ Though simple and easily reproducible, the method is inconvenient for patients, and it may be cumbersome to use in a clinical setting, especially with respect to

Limb circumference as measured by a non-elastic tape measure has also been used as a surrogate for differential limbs' volumes. These measurements can be taken at specified anatomical landmarks or at regular intervals along the length of the limb.¹² Though cut-offs may vary by method, a difference of 2 cm between limbs is considered diagnostic of lymphedema.^{13 14} This method is inexpensive and easily taught, which makes it attractive. However, the measurements are often not sensitive enough to detect small changes: furthermore they require a normal contralateral limb, which may not be possible in the setting of bilateral disease.¹² Mathematical formulae have also been used to correlate a series of standard tape measurement to volumes. The most commonly used is the Frustum Formula, which calculates volume by assuming that limbs are similar to cones. These methods attempt to maximize the simplicity of tape measurements and the utility of comparing volumes: they are not sets of linear measurements.¹⁵

A perometer is a more complex tool that utilizes parallel light-emitting diodes to measure corresponding extremity diameter throughout the length of the limb, allowing for volumetric assessment without using water displacement. Perometry has demonstrated higher interobserver reliability compared with tape measurements, especially for clinicians who do not regularly do such assessments.¹⁴ However, the high cost of this diagnostic tool prohibits its widespread use, especially in a clinical setting where many of these assessments are done.¹⁰

Other diagnostic modalities that examine intrinsic tissue changes include bioimpedance spectroscopy and tissue tonometry. Bioimpedance spectroscopy exploits the fact that edematous tissues have higher water content and a lower tissue resistance. Differential measurement of this resistance allows for an estimation of extracellular water volume as a surrogate marker for lymphedema.¹⁶ Bioimpedance spectroscopy enables the detection of subclinical lymphedema and may facilitate interventions to reduce the likelihood of the disease entering the irreversible stages. Importantly, bioimpedance spectroscopy technology does not require an internal control. This is relevant in the setting of gynecologic malignancy, where bilateral disease is more common.⁴ Tissue tonometry objectively measures the resistance of soft tissue to compression, thus acting as a surrogate for edema and tissue fibrosis changes in lymphedema. However, this technology also requires an internal

Which of the following statements regarding lymphedema diagnosis is false:

- Limb volume measured by water volumeter is the gold standard but is inconvenient for patients
- A difference of 2cm in limb circumference between limbs is diagnostic of lymphedema
- The Frustum formula calculates volume by assuming that limbs are similar to cones
- A perometer uses light emitting diodes in series to measure extremity diameter throughout the length of the limb and has high interobserver variability
- Other diagnostic modalities include bioimpedance spectroscopy and tissue tonometry

Imaging studies can also be used in difficult-to-diagnose cases of lymphedema, as well as in staging and surgical treatment planning. The traditional oil contrast lymphography—an x-ray-based imaging modality—has been largely replaced by radionuclide lymphangioscintigraphy, whereby an intradermal injection of a radionuclide such as Technetium-99 is used to provide qualitative information on the lymphatic system as well as quantitative data on lymph transit times.¹⁸ Single-photon emission CT similarly uses a dermally injected radionuclide and gamma rays to visualize the lymphatic system. The extent of dermal backflow is better visualized by this method, compared with lymphoscintigraphy. Similarly, gadolinium-based contrast can be injected dermally to visualize lymphatics and the surrounding soft tissue using MRI.¹¹ Near infrared imaging using indocyanine green—a technology best known for its use in the intraoperative identification of sentinel lymph nodes in cancer staging—has also been utilized to visualize lymphatic patterns and the active contractility of lymphatic vessels in real time.¹² This can be particularly helpful intraoperatively, and in the diagnosis of lymphatic dysfunction prior to the onset of lymphedema. At the present time, however, the availability of this technology is limited.¹⁸

It should be noted that not every change in limb circumference, volume, or abnormal imaging study is indicative of clinically significant lymphedema. Additionally, lymphedema symptoms may be reported by patients before they become clinically identifiable through circumference or volume changes (ie, leg heaviness). That is why several studies have focused on patient-reported lymphedema, using validated surveys with good sensitivity and specificity for diagnosing clinically significant lower leg lymphedema. Larger studies comparing patient-reported outcomes to objective metrics are still needed.¹³ The Gynecologic Oncology Group study 244 (GOG 244), also known as the Lymphedema and Gynecologic (LEG) cancer study, is a prospective multicenter trial which examines both objective measurement and patient-reported surveys to better our understanding of the true burden of lymphedema in patients with gynecologic malignancy.¹⁹

Once a diagnosis of lymphedema is established, staging should be done to determine the proper treatment regimen and quantify treatment response. The International Society of Lymphology (ISL) stages of lymphedema are summarized in [Table 1](#) and shown in [Figure 1](#). This system takes into consideration both qualitative stage and quantitative physical assessment (ISL Grade) which allows for streamlined diagnosis and the monitoring of treatment response.¹⁰ However, in its 2016 statement on the grading system, the Society states that a “more detailed and inclusive classification needs to be formulated”, one that would ideally take genotypic information, disability grading, assessments of inflammation, and imaging modalities into consideration.¹⁰ The National Cancer Institute’s common terminology criteria for adverse events (CTCAE) is often used to stage secondary lymphedema in both research and clinical settings ([Table 1](#)). However, these grades focus on the physical impediments that patients encounter rather than on objective measures, making them unreliable in the diagnosis of true lower extremity lymphedema.²⁰

SECONDARY LYMPHEDEMA IN GYNECOLOGIC MALIGNANCIES

To date, the preponderance of research on lymphedema within the field of oncology has focused on upper extremity lymphedema in patients treated for breast cancer. These data have facilitated the development of diagnostic and treatment strategies for lymphedema and have altered the clinical care of breast cancer patients by incorporating sentinel lymph node dissection into the treatment algorithm. Despite these promising strides, lymphedema in other anatomical sites remains under-recognized and understudied. In addition, there are obvious differences in the upper and lower extremities with respect to tissue composition and mechanical functioning; therefore, extrapolating data based on the upper extremities should be done with caution. In the next part of this review we focus on lower extremity lymphedema and how it affects

Imaging used in difficult to diagnose cases includes oil contrast lymphography, radionuclide lymphangioscintigraphy, dual photon emission CT and non contrast MRI.

- a. True
- b. False

Lymphedema symptoms may be reported by patients before they are clinically measurable

- a. True
- b. False

Once diagnosed lymphedema should be staged using the National Cancer Institute’s common terminology criteria for adverse events

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- a. True
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patients with endometrial cancer, ovarian cancer, vulvar cancer, and cervical cancer.

Lymph from the gynecologic organs primarily drains into the three lymph node beds: pelvic, para-aortic, and inguinofemoral. These basins are often sampled or completely excised as part of the surgical management of gynecologic malignancies. Overall, the incidence of treatment-related lymphedema is about 25%, but it may be as high as 70% in some patient populations.²¹ There are two consistent contributors to lower extremity lymphedema in these patients: lymphadenectomy and radiation therapy. Lymphadenectomy—defined as complete excision of a lymph node basin—directly disrupts the normal return of lymphatic fluid from the lower extremities. In general, the risk of lymphedema is proportional to the number of lymph nodes sampled, with the excision of certain lymph nodes and lymph node basins thought to present a higher risk.²² Sentinel lymph node mapping alone has been shown to decrease the risk of lower extremity lymphedema to less than 10%, across gynecologic malignancies.²¹ Radiation-induced lymphedema is thought to be secondary to lymph node and lymphatic vessel sclerosis, scarring, and subsequent impedance of upstream lymphatic flow. A systematic meta-analysis of all studies examining radiation and risk of lower extremity lymphedema in gynecologic cancer found the risk to be 34% in patients receiving radiation treatment.²¹

The two consistent contributors to lower extremity lymphedema are lymphadenectomy and radiation therapy

- a. True
- b. False

The risk of lymphedema is proportional to the number of lymph nodes sampled

- a. True
- b. False

Sentinel lymph node mapping alone decreases the risk of lower limb lymphedema to <3%

- a. True
- b. False

More than one third of patients have lower limb lymphedema following radiation therapy

- a. True
- b. False

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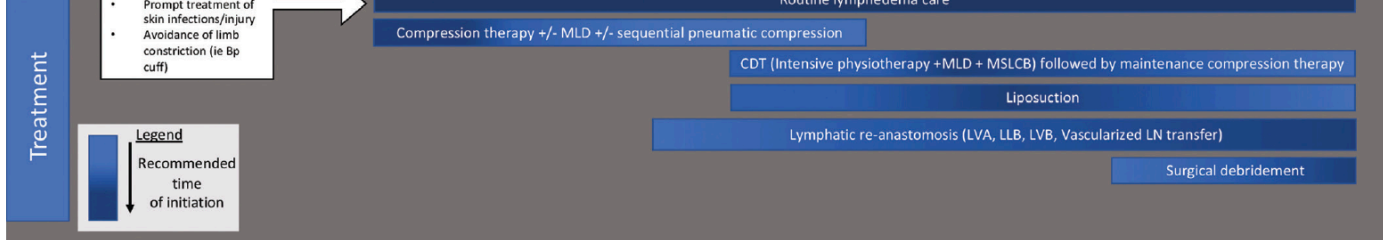


Figure 2 Summary algorithm for the treatment of lymphedema. All patients should be evaluated for the risk of lymphedema prior to treatment for gynecologic malignancies and appropriate steps taken during treatment to reduce their risk, if possible. Patients should then be evaluated for lymphedema post-treatment. If clinically suspicious limb edema is present, other etiologies should be ruled out (Box 1), with the help of imaging or diagnostic modalities described in table 2 as needed. Once lymphedema is diagnosed and appropriately staged, treatment is tailored to the patient stage, with more aggressive measures usually taken at higher stages. LEL, lower extremity lymphedema; MLD, manual leg decompression; LVA, lymphaticovenous anastomosis; LLB, lymphatic-lymphatic bypass; LVB, lymphaticovenous anastomosis; LN, lymph node; CTD, complete decongestive therapy.

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Cervical cancer

Worldwide, the median age of diagnosis of cervical cancer is mid- to late 40s. At the time of diagnosis and treatment, 45% of patients have stage 1 disease, with a 5-year overall survival rate of 79%–98%.²³ Minimizing the long-term risks of lower extremity lymphedema in this relatively young patient population is particularly important. The management of early-stage cervical cancer typically involves a radical hysterectomy and lymph node assessment, either by pelvic lymphadenectomy with or without para-aortic lymphadenectomy, or by sentinel lymph node mapping. Prior to the introduction of sentinel lymph node mapping, the rates of treatment-related lower extremity lymphedema ranged from 10%²⁴ when assessed retrospectively to 41%²⁵ when prospectively assessed using objective metrics. The rates of lower extremity lymphedema after fertility-sparing surgery with radical trachelectomy fall within this range at 24%, as lymphadenectomy is also done in these cases.²⁶

Radiation contributes to lower extremity lymphedema. This is significant because chemoradiation is the standard of care for locally advanced cervical cancer, and adjuvant radiation is used in intermediate- and high-risk patients after radical hysterectomy and lymphadenectomy or sentinel lymph node mapping. The combination of surgery and radiation appears to be particularly detrimental. Landoni et al reported the results of a randomized trial comparing

Rates of lower extremity lymphedema may be as high as 41% after radical hysterectomy and pelvic lymphadenectomy for cervical cancer when assessed prospectively using objective measures.

- True
- False

A combination of surgery and radiation does not increase the risk of lower extremity lymphedema compared to surgery alone or radiation alone

- True
- False

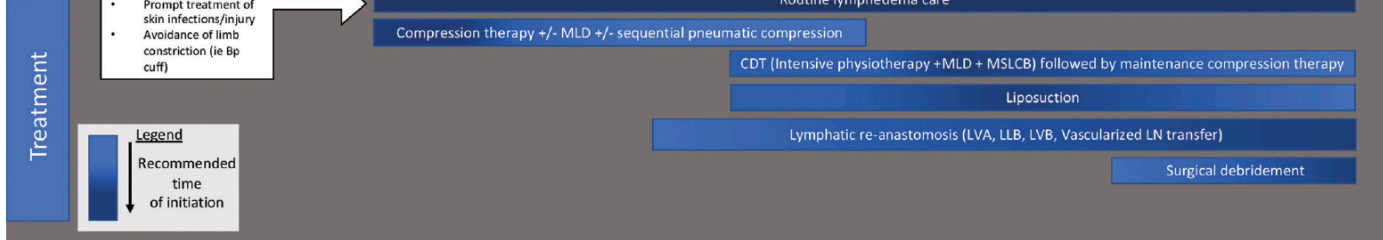


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98% negative predictive value in prospective trials.²⁹ Niikura et al found that lower extremity lymphedema rates decreased from 42% to 8.7% using their sentinel lymph node mapping algorithm.³⁰ SENTICOL III (International Validation Study of Sentinel Node Biopsy in Early Cervical Cancer), a large prospective, multicenter randomized trial examining the validity of sentinel lymph node mapping in cervical cancer, is currently underway.³¹

Endometrial cancer

Lymph node assessment in endometrial cancer is an important part of surgical management. The published risk of lower extremity lymphedema in endometrial cancer ranges widely, from 1.2% in retrospective analyses³² to 47% in prospective studies utilizing quality-of-life surveys.³³ Risk factors for the development of the most common histology in endometrial cancer (endometrioid adenocarcinoma), including obesity and metabolic syndrome, are also risk factors for the development of lower extremity lymphedema due to etiologies such as chronic venous insufficiency and congestive heart failure. Thus, this population may have higher rates of baseline lower extremity lymphedema that can be mistaken for, or exacerbated by, malignancy. In a study by Abu-Rustum et al assessing rates of postoperative lower extremity lymphedema in endometrial cancer patients prior to the introduction of sentinel lymph node mapping, 5%–6% of patients had clinically reported lower extremity lymphedema preoperatively, potentially secondary to another comorbidity.³² Obesity, a comorbid condition in a large

Patients with endometrial cancer are at risk of lower extremity lymphedema because

- a. They have higher rates of chronic venous insufficiency
- b. They have higher rates of congestive heart failure
- c. They have higher rates of baseline lower extremity lymphedema
- d. They are more likely to be obese
- e. All of the above

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percentage of endometrial cancer patients, makes lymphedema clinically harder to detect in its early stages and can independently contribute to its pathogenesis.³³ Lipedema, the disordered deposition of fat under the skin, can affect an overlapping population as endometrial cancer, i.e. peri/post-menopausal obese women, making the exclusion of this diagnosis in this population particularly important. These patients will have more painful, non-pitting edema which spares the feet and is incited by hormonal shifts (puberty, pregnancy, menopause etc.) and is associated with a family history of the disorder.¹

In endometrial cancer, as in cervical cancer, the number of lymph nodes removed at the time of lymphadenectomy is associated with the risk of lymphedema, though an exact threshold has not been established.^{33,34} In a published series from our institution, all cases of lower extremity lymphedema were in patients with greater than 10 lymph nodes sampled.³² However, the presence of lower extremity lymphedema was determined by reviewing medical records, which underestimates the true rate of this condition, making it difficult to draw definitive conclusions. The presence of metastatic disease in lymph nodes is also associated with the development of lower extremity lymphedema even after authors controlled for the performance of lymphadenectomy, suggesting that lymphatic metastasis may independently contribute to later lymphatic dysfunction.³⁵

The acceptance of sentinel lymph node mapping as a standard in the staging of endometrial cancer provides a method for reducing morbidity secondary to lymphadenectomy. Prospective multicenter trials have demonstrated a sensitivity of 97.3% and negative predictive value of 99.6% using sentinel lymph node mapping.³⁶ This method has already been shown to decrease the rates of lower extremity lymphedema. Geppert et al noted that, in patients who underwent sentinel lymph node mapping compared with patients undergoing full lymphadenectomy, the rates of lymphedema (as prospectively diagnosed by a physiotherapist) were significantly lower: 1.3% vs 18.1% ($P=0.0003$).³⁷ However, the exact method of diagnosis was unclear. We have presented the results of a study conducted at our institution assessing the prevalence of patient-reported lower extremity lymphedema after surgery for gynecologic cancer. The patient-reported rate was significantly lower in those who had undergone a sentinel lymph node mapping procedure per our institutional algorithm, compared with those who had undergone bilateral lymphadenectomy (27 vs 41% respectively).

The risk of lower extremity lymphedema in patients with endometrial cancer depends on:

- a. The number of lymph nodes sampled
- b. If greater than 8 lymph nodes sampled
- c. The co-existence of lipedema
- d. Pre-menopausal status
- e. Family history

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Ovarian cancer

The lowest rate of lower extremity lymphedema is reported in ovarian cancer patients, ranging from 4.7% in a retrospective study³⁸ to 30.4% in prospective patient-reported surveys.³⁹ Again, lymphadenectomy is the most important prognostic factor.^{38 39} In ovarian cancer, surgical evaluation of the pelvic nodes and para-aortics up to the renal vessels is considered the standard of care for early-stage disease confined to the ovary and/or pelvis.⁴⁰ Lim et al examined a cohort of ovarian cancer patients with early-stage disease, 97.2% of whom underwent lymphadenectomy, and reported that 55% had lymphedema. It should be noted that 57.4% had greater than 35 lymph nodes excised.⁴⁰ The majority of patients with newly diagnosed ovarian cancer actually present with advanced stage disease, in which case such a systematic lymphadenectomy is not routinely performed except in the setting of grossly enlarged nodes.⁴¹

Patients with advanced stage ovarian cancer are at risk of lower extremity lymphedema because they require systematic lymphadenectomy

- a. True
- b. False

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Patients with advanced stage ovarian cancer are at risk of lower extremity lymphedema because they require systematic lymphadenectomy

- a. True
- b. False

Vulvar cancer

Vulvar cancers, compared with other gynecologic malignancies, have a more reliable and predictable lymphatic drainage to the inguinofemoral nodal basins. Rates of lower extremity lymphedema after inguinofemoral lymphadenectomy range from 10% in retrospective reports⁴³ to 73% in studies assessing patient-reported symptoms.⁸ In studies using a uniform methodology to diagnose lower extremity lymphedema across types of malignancy, the rates are consistently highest in vulvar cancer: based on a recent meta-analysis, the pooled incidence is 28.8%.^{5 39 44} This is mostly, but not entirely, related to inguinofemoral lymphadenectomy.⁴³ Berger et al reported that 6.7% of patients with vulvar cancer treated with radiation alone developed chronic lower extremity lymphedema.⁴³ Other risk factors include infection, extensive lymph node dissection, and postoperative adjuvant radiation therapy.⁴⁴ A small series have suggested possible ways to prevent lower extremity lymphedema after lymphadenectomy. Dardrian et al reported that sparing the saphenous vein decreased rates of clinically identified lower extremity lymphedema from 38% to 11% ($P < 0.05$).⁴⁵ Other surgical techniques associated with decreased rates include omental flaps, prophylactic diverting lymphatic microsurgery, and fascia-preserving dissections.⁴⁶ Sentinel lymph node mapping is now considered an acceptable method for nodal assessment in vulvar cancer. It has been prospectively assessed by the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINNS) study group as well as the GOG, and has demonstrated acceptable reliability in determining nodal status.^{47 48} In a large single-arm prospective study, the rate of lower extremity lymphedema after sentinel lymph node mapping was 1.9%, compared with 25.3% after lymphadenectomy ($P < 0.05$).⁴⁹ It should be noted that patients undergoing treatment for gynecologic malignancies can also suffer from lymphedema isolated to the pelvis or the perineum (particularly with vulvar cancers). Pelvic/genital lymphedema may present with similar heaviness and pressure in the pelvic floor with minimal or no leg manifestations. Treatment of this patient populations is particularly difficult and centers around pelvic harnesses and surgical management.⁵⁰

Studies assessing patient-reported symptoms have shown rates of lower extremity lymphedema after inguinofemoral lymphadenectomy for vulvar cancer of:

- a. 10%
- b. 73%
- c. 28.8%
- d. 6.7%

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Which of the following has **not** been shown to prevent lower extremity lymphedema in vulvar cancer surgery:

- a. Sparing the saphenous vein
- b. Omental flaps
- c. Diverting lymphatic microsurgery
- d. Sentinel lymph node mapping
- e. Fascia-preserving surgery
- f. Radiation alone

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- c. Diverting lymphatic microsurgery
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- e. Fascia-preserving surgery
- f. Radiation alone

In a small study of highly selected patients undergoing lymphadenectomy, prophylactic lymphovenous anastomosis and shunts have demonstrated efficacy, though its applicability on a larger scale is unknown at this time.⁵⁴ Omental (gastroepiploic) free flaps containing lymph node bundles have been described for the management of patients with secondary lymphedema in the upper and lower extremities.⁵⁵ The procedure might prove useful as a preventative measure at the time of inguinofemoral lymphadenectomy. We have been considering this option at our institution. However, there is currently no data that would provide recommendations.

Additional strategies to prevent lower extremity lymphedema focus on early identification of stage 0 and 1 lymphedema, in which skin changes are absent and edema is reversible. Educating patients about the symptoms may facilitate early diagnosis. Beesley et al reported that in 802 gynecologic oncology patients without diagnosis of lower extremity lymphedema, 15% had some symptoms that warranted further evaluation.³⁸

The ISL recommends specific interventions to reduce progression and limit long-term sequelae for patients with early or subclinical lymphedema.¹⁰ These measures are not all evidence-based, rather they are based on the biology of lymphedema and the reduction of potential risk factors for progression. Early conservative management includes encouraging lymphatic flow into the venous system and avoiding lymphatic stasis that causes fibrosis and further damage. This can be achieved by elastic hosiery or non-elastic compression leggings in patients with stage 0 or mild stage 1 lower extremity lymphedema.¹⁰ In patients with more clinically significant edema, multiple layers of short-stretch compression bandages has been prospectively shown (by Badger et al) to decrease leg volume by an additional 15.3% compared with compressive hosiery alone (P=0.001).⁵⁶ The next phase of treatment for persistent edema that does not respond to simple compression involves mechanical and targeted displacement of lymphatic fluid from tissues. Traditionally this has been done by manual lymphatic draining and sequentially intermittent pneumatic compression. Manual lymphatic drainage is specialized physiotherapy utilizing targeted massage and limb movements that stimulate the flow of lymphatic fluid out of damaged tissues to tissues with intact lymphatic drainage.¹¹ Both of these measures have proven to be good adjuncts to compressive garments and bandaging in mild to moderate breast cancer-related lymphedema, and this has been recapitulated in smaller observation studies focusing on lower extremity lymphedema.⁵⁷

Some small randomized, controlled trials suggest that manual lymphatic drainage may not provide a significant amount of volume reduction beyond wrapping alone.⁶⁰ Furthermore, the continued benefits of limb volume reduction depends on patient compliance with maintenance therapy.

There are some surgical and invasive interventions that can be considered to prevent or treat lower extremity lymphedema. Multiple microsurgical techniques have been investigated.^{54 61} The core concept is restoration of normal lymphatic drainage, whether by anastomosing lymphatics to each other (lymphatic-lymphatic bypass), anastomosing afferent lymphatics to the venous circulation (lymphovenous bypass), creating anastomoses between subdermal lymphatic and venules (lymphaticovenular anastomosis), or transplanting vascularized lymph node bundles.⁶¹ These methods all have varying degrees of success. Campisi et al reported on 1800 cases of lower and upper primary and secondary edema (>90% stage II and III) managed with various lymphatic/venous bypass, using native tissues to the lymph node bed or autologous venous grafting.⁶² Corrective procedures were most commonly performed in the sub-inguinal region. In this patient population, 87% had subjective improvement of symptoms, 83% had objective reduction in limb volume, and 85% were able to discontinue other conservative treatments.⁶² Allographic vascularized nodal tissue transplantation has also been utilized. Theoretically, after anastomosis with blood vessels in the receipt lymphatic bed, the vital nodal tissue will form new lymphatic connections via lymphangiogenic mechanism. This should lead to improved afferent lymphatic drainage. In patients with lower extremity lymphedema, limb circumference reductions of 46%–64% are reported, with documented improvement in lymphatic flow as assessed with indocyanine green lymphography and/or lymphoscintigraphy.^{61 63} A potential drawback of this method is the risk of lymphedema in the afferent limb or tissue of the donor site, which in lower limbs often includes the inguinal or supraclavicular lymph nodes.⁶³ A meta-analysis of 27 studies focusing on lymphovenous shunting and vascularized lymph node transplantation reported an average reduction in lower limb circumference of 57%, which is greater than that reported for the upper extremities (46%). It is important to note that this meta-analysis was not based on randomized trials and, as always, proper patient selection is critical.⁶⁴

Other surgical methods focus on the removal of abnormal tissues. Early lymphedema results in excessive adipose tissue propagation, which cannot be treated with fluid decompression

Techniques to prevent lower extremity lymphedema include:

- a. Lymphovenous anastomosis and shunts
- b. Gastroepiploic free flaps
- c. Early identification of lymphedema
- d. All of the above

There is high quality evidence for all of the above interventions

- a. True
- b. False

Early conservative management for stage 0 or mild stage 1 lower extremity lymphedema includes

- a. Elastic hosiery or non-elastic compression leggings
- b. Short stretch compression bandages
- c. Targeted massage

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Early conservative management for stage 0 or mild stage 1 lower extremity lymphedema includes

- a. Elastic hosiery or non-elastic compression leggings
- b. Short stretch compression bandages
- c. Targeted massage

More significant lymphedema must often be managed by more intensive, multimodal treatment, collectively described as complete decongestive treatment. This includes a combination of intensive regular physiotherapy, manual lymphatic drainage, and multilayer short-stretch compression bandaging. Once a plateau of response is identified, the maintenance of treatment response is obtained using daily limb compression with compression garments and continued skin and nail hygiene.¹¹ Prospective data shows about a 60% reduction in limb volume using this method in moderate to severe lymphedema.⁵⁸ Kim et al demonstrated that complete decongestive treatment not only improved lower limb volume but also improved quality of life metrics.⁵⁹ However, given the variation in complete decongestive treatment regimens and the heterogeneity of the patient populations in these studies, it is difficult to precisely determine which part of the therapy is most efficacious. Some small randomized, controlled trials suggest that manual lymphatic drainage may not provide a significant amount of volume reduction beyond wrapping alone.⁶⁰ Furthermore, the continued benefits of limb volume reduction depends on patient compliance with maintenance therapy.

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Management of more significant lymphedema involves multimodal decongestive treatment including intensive regular physiotherapy, manual lymphatic drainage and multilayer short-stretch compression bandaging, and skin and nail hygiene.

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Microsurgical techniques to prevent/treat lower extremity lymphedema include:

- a. Lymphatic-lymphatic bypass
- b. Lymphovenous bypass
- c. Lymphovenicular anastomosis
- d. Vascularized lymph node bundle transplant
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All of the above techniques have proven efficacy in the prevention/treatment of lower extremity lymphedema based on high quality randomized trials.

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CONCLUSION

Secondary lower extremity lymphedema causes significant morbidity for survivors of gynecologic cancers. Lack of uniform assessment and diagnosis has led to difficulty in identifying the true rates of lymphedema. However, data has shown that patients with vulvar cancers, those undergoing lymphadenectomy, and those treated with radiation are at the highest risk. Early identification of at-risk populations and patient education regarding early symptoms may aid in prevention, early diagnosis, and treatment. Standardized methods for identifying at-risk patients (predictive risk factor model and symptom assessment) and improved provider education (accurate incidence and risk factor data) are greatly needed to address these issues. Newer, more objective measures, including patient-reported outcomes, can aid in the diagnosis and monitoring of treatment response. It is essential that we continue to introduce surgical techniques that place patients at the lowest possible risk and avoid high-risk procedures whenever possible. Prevention, early diagnosis, and timely interventions are key, but more research is needed to help us better understand lower extremity lymphedema. Patients who appear to be developing this condition should be referred in the early stages, when intervention has a greater chance of success. With risk mitigation, early diagnosis, and appropriate treatment, we can improve the quality of life for patients burdened by lower extremity lymphedema secondary to the treatment of gynecologic malignancies.

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Competing interests None declared.

Rates of lower extremity lymphedema in gynecologic cancer survivors are difficult to measure due to lack of uniform assessment and diagnosis.

- a. True
- b. False

Highest risk patients are those undergoing lymphadenectomy and radiation therapy

- a. True
- b. False

Early identification and patient education about symptoms may aid in prevention, early diagnosis and treatment

- a. True
- b. False

Patients who appear to be developing lymphedema should be observed and only referred for treatment when their symptoms become more severe

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Contributors All authors contributed to the conception and design, drafting, and critical revision of this manuscript. All authors have given final approval of this version to be published, and all authors accept responsibility for its contents.

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Further Reading

- [GOG 244-The lymphedema and gynecologic cancer \(LEG\) study: Incidence and risk factors in newly diagnosed patients.](#) Carlson JW, Kauderer J, Hutson A, Carter J, Armer J, Lockwood S, Nolte S, Stewart BR, Wenzel L, Walker J, Fleury A, Bonebrake A, Soper J, Mathews C, Zivanovic O, Richards WE, Tan A, Alberts DS, Barakat RR. Gynecol Oncol. 2019 Dec 11. pii: S0090-8258(19)31566-5. doi: 10.1016/j.ygyno.2019.10.009. PMID: 31837831

Further Reading

- [GOG 244 - The LymphEdema and Gynecologic cancer \(LEG\) study: The association between the gynecologic cancer lymphedema questionnaire \(GCLQ\) and lymphedema of the lower extremity \(LLE\).](#)
Carter J, Huang HQ, Armer J, Carlson JW, Lockwood S, Nolte S, Stewart BR, Kauderer J, Hutson A, Walker JL, Fleury AC, Bonebrake A, Soper JT, Mathews C, Zivanovic O, Richards WE, Tan A, Alberts DS, Barakat RR, Wenzel L. Gynecol Oncol. 2019 Dec;155(3):452-460. doi: 10.1016/j.ygyno.2019.09.027. PMID: 31679787