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Review Article

# Lower limb lymphedema after surgical staging for endometrial cancer: Current insights and future directions

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ABSTRACT

Lower extremity lymphedema (LEL) is a common complication following surgical staging of endometrial cancer. LEL is a chronic condition associated with significant impact on patient morbidity and quality of life (QoL). This review aimed to report the current evidence in the literature on secondary LEL after surgical staging for endometrial cancer, focusing on the incidence based on different approaches to lymph node staging, diagnosis, risk factors, and the impact on QoL. Due to the absence of a standardized agreement regarding the methodology for evaluating LEL, the documented frequency of occurrence fluctuates across different studies, ranging from 0% to 50%. Systematic pelvic lymphadenectomy appears to be the primary determinant associated with the emergence of LEL, whereas the implementation of sentinel lymph node biopsy has notably diminished the occurrence of this lymphatic complication after endometrial cancer staging. LEL is strongly associated with decreased QoL, lower limb function, and negative body image, and has a detrimental impact on cancer-related distress reported by survivors. Standardization of lymphedema assessment is needed, along with cross-cultural adaptation of subjective outcome measures for self-reported LEL. The advent of sentinel lymph node mapping represents the ideal approach for accurate nodal assessment with less short- and long-term morbidity. Further research is needed to definitively assess the prevalence and risk factors of LEL and to identify strategies to improve limb function and QoL in cancer survivors with this chronic condition.



## Introduction

Endometrial cancer (EC) is the most common gynecological tumor in developed countries, and its incidence is rising. It is estimated that 66,200 new uterine cancer cases are occurring in 2023, with 13,030 deaths in the United States [1]. The majority of patients present with clinically early-stage disease and a subsequent good prognosis. However, lymphatic metastasis occurs in 10–15% of the patients, severely impacting the oncologic outcomes [2]. Given that the status of lymph nodes is a critical prognostic factor that strongly influences the selection of appropriate adjuvant treatments, the evaluation of lymph nodes through surgical staging holds significant importance [3]. Although two prospective trials showed no survival benefit of lymphadenectomy (LND) in cases of apparent early-stage EC, nodal assessment for staging purposes still has paramount diagnostic and prognostic value [4,5]. During the recent years, sentinel lymph node (SLN) mapping has been

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introduced as a less invasive alternative to LND for retroperitoneal staging of EC patients [6,7]. The National Comprehensive Cancer Network guidelines have included the SLN algorithm as a valid option for all patients with EC [8], even for high-risk EC patients [7,9]. However, one of the main complications related to the dissection of the pelvic lymph node tissue is the risk of developing lower extremity lymphedema (LEL) [10].

Postsurgical lymphedema, classified as "secondary lymphedema," is a common consequence of the removal of lymph nodes or injuries to the lymphatic vessels during the procedures, resulting in lymphatic insufficiency and inadequate lymph transport. Decreased lymph transport leads to an accumulation of protein-rich interstitial fluid, and subsequent swelling and progressive fibrosis. Since lymphedema represents a dynamic condition, progressive lymphedema can lead to functional impairment, which could range from being asymptomatic to severely compromise mobility and daily function with the potential to be extremely disfiguring [11]. Moreover, lymphedema is associated with a significant worsening of quality of life (QoL) in EC survivors [12]. However, some patients with EC are candidates for adjuvant treatment with radiotherapy or a combination of treatment modalities, which has a potential adverse effect on the worsening of this clinical condition owing to radiotherapy-induced fibrosis [13].

The prevalence of LEL among patients with EC varies widely across studies, with an estimated rate between 0% and 50% [13–15]. On the one hand, unfortunately lymphedema is still a poorly known and understudied complication, and research on LEL after surgical lymph node dissection most often fails to differentiate between different gynecologic cancers.

On the other hand, the heterogeneity of the available studies in terms of methods for LEL diagnosis (objective evaluation vs. subjective evaluation) [16,17] contributes to the lack of definitive data on the prevalence of this complication [18]. Despite several evolutions of the surgical management of EC patients [6,19], there is still a high rate of cancer survivorship struggles with lower limb lymphedema. The aim of this current review is to summarize the available evidence about lower limb lymphedema after surgical staging for endometrial cancer.

## Diagnosis

A prompt diagnosis is one of the main challenging aspects of LEL after gynecologic cancer surgery. Early signs and symptoms are often unrecognized, especially in morbidly obese patients, leading to a difficult and delayed diagnosis. Furthermore, the best diagnostic method for LEL has not been established yet, and a standardized workup for lymphedema diagnosis is not still validated [16,17,20,21].

In Gynecologic Oncology Group (GOG) study 244, LEL has been objectively diagnosed as a limb volume change (LVC) of at least 10%, comparing the preoperative circumferential measurements to at least one postoperative measurement. Measurements of the limb were obtained by taking bilateral circumferential measurements at 10-cm intervals starting 10 cm above the bottom of the patient's heel and continued to the inferior aspect of the inguinal crease of the groin. This objective method represents a valid surrogate for lymphedema [15]. Submersion of the lower limb with water displacement assessment has been considered the gold standard for evaluating limb volume change (LVC). Nonetheless, this approach is challenging, and far to be implemented in routine clinical settings [22]. An identifying and distinctive indication of lymphedema is the presence of Stemmer's sign. This diagnostic maneuver involves gripping a skin fold at the base of the second toe on both feet, with a positive result indicating the inability to lift the skin fold, thus confirming the presence of lymphedema. In addition to direct measurements, imaging methods and technologies have also been used [23].

Magnetic Resonance Imaging (MRI) has recently been showing an emerging role in diagnosing lymphedema. It offers several advantages by providing information on the anatomy of the lymph stagnated vasculature and high resolution of soft tissue edema. Moreover, the MR lymphography (MRL) technique allows the study of deep and superficial lymphatic vessels following the subcutaneous injection of MR contrast agents [24]. Bioimpedance spectroscopy represents an effective tool to detect LEL by measuring the impedance of extracellular and intracellular water to an alternating electrical current passed through the body at a range of nondiscernible frequencies. However, since this method is based on comparing both limbs, there are no standardized criteria in cases of bilateral LEL [25].

Regards subjective evaluation, signs and symptoms of LEL are often reported first by the patients. Thus, exploring patient-subjective outcomes represents a valid tool for diagnosing LEL. Although several studies have introduced questionnaires to investigate the health-related QoL among gynecologic cancer survivors, few items were included for assessing symptoms specific to lymphedema.

A dedicated questionnaire for LEL, including 13 specific items, was developed and validated by investigators from the Mayo Clinic [26]. This tool showed a high sensitivity (95.5%) and specificity (86.5%) for detecting LEL when a cut-off $\geq$5 points was used. Moreover, the sensitivity and specificity were 94.8% and 76.5%, respectively, considering participants who were obese (Body Mass Index, BMI> 30 kg/m$^2$).

A specific scale for evaluating LEL in gynecologic cancer patients was initially introduced by adapting the Lymphedema Breast Cancer Questionnaire (LBCQ) [27]. The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) is a 20-items self-reporting tool that measures seven symptom clusters-aching, heaviness, infection-related, numbness, physical functioning, general swelling, and limb swelling. In detail, more patients with a $\geq$4 point increase in total GCLQ score were diagnosed with LEL compared to those not diagnosed with LEL ($p < 0.001$). The clinical cut-off score of a 4-point increase from baseline yielded a sensitivity and specificity of >60% [18].

Although these validated self-reported screening questionnaires are emerging tools, their translated and cross-cultural adaption across different countries is still lacking. However, uniformly using the same method is crucial to reduce the risk of introducing bias into a study and accurately comparing results. In this scenario, Bjerre Trent et al. have recently shown that the translation process and cross-cultural adaptation of subjective outcome measures for self-reported LEL into a non-English language is feasible [28]. Indeed, patient-reported lymphedema symptoms represent an efficient tool to differentiate patients with and without an LLE diagnosis. Assessing lymphedema through subjective evaluation represents a simple, feasible, and time-efficient method, yielding a routine incorporation into the clinical care setting.

## Lower extremity lymphedema: systematic pelvic lymphadenectomy and sentinel lymph node

The introduction of extensive LND in the clinical practice for the surgical management of apparent early-stage EC is associated with increased morbidity [29]. Although LEL represents the most common type of lymphatic complication, studies have often lacked baseline information and details on the method used to determine lymphedema. The ASTEC trial [4] and the Italian collaborative trial [5] reported a higher prevalence of LEL in patients with LND (3.4% and 13%, respectively) compared to patients without LND (0.3% and 1.6%, respectively). However, the primary endpoint of the two RCTs

was the assessment of survival outcomes (overall and recurrence free survival) associated with retroperitoneal staging, with no specific focus on LEL. In a study by the Mayo Clinic [30], comparing systematic pelvic with and without aortic lymphadenectomy to a simple hysterectomy for EC, 591 responders to the validated 13-item lymphedema screening questionnaire were included. The overall prevalence of LEL was 47.0% with a median 6.2-year follow-up, and the specific rates in patients treated with hysterectomy alone compared with lymphadenectomy were 36.1% and 52.3%, respectively (attributable risk 23%).

Recently, the Gynecologic Oncology Group (GOG) 244 reported the results of a trial designed to prospectively estimate the incidence of LEL among a large cohort of gynecologic cancer patients (endometrial, cervical, or vulvar malignancy) undergoing radical surgery with LND [15]. The patients received a baseline assessment followed by sequential evaluation for LEL using objective measurements (bilateral circumferential measurements) over a 2-year interval. LEL was defined as a LVC >10% from baseline and classified as mild, moderate, and severe (10–19% LVC; 20–40% LVC; >40% LVC, respectively). The incidence of LEL was 34% in the EC cohort, and LVC was classified as mild in 22.8%, moderate in 9.5%, and severe in 1.4% of EC patients.

Few studies reported the LEL outcome after SLN biopsy only, and the reports compared SLN to systematic LND regarding the prevalence of this postoperative lymphatic complication. Overall, SLN results in a lower incidence of LEL, representing a protective factor (Table 1).

Leitao et al. [31] compared the outcome of 180 EC patients who had SLN vs. 352 LND vs. 67 who had hysterectomy alone. The patients were mailed the Mayo Clinic questionnaire of validated 13-item LEL screening survey and a validated QoL assessment tool. This report from Memorial Sloan Kettering Cancer Center (MSKCC) represents the first study to assess patient-reported LEL after SLN mapping for newly diagnosed EC. The lymphedema prevalence rate was 27.2% (49/180; 95% CI, 20.7e33.7%) and 40.9% (44/352; 95% CI, 35.8e46.1%) in the SLN cohort and LND, respectively. Furthermore, self-reported LEL prevalence was 40.3% (27/67; 95% CI, 28.6e52.0%) among the patients who had hysterectomy alone. Recently, investigators from Mayo Clinic conducted a study on 378 EC patients distributed in two cohorts based on the lymph nodal assessment: LND vs SLN using the Mayo Clinic LEL PRO tool. One-hundred twenty-seven (33.5%) patients underwent SLN with or without side-specific LND (sentinel lymph node cohort), while 251 (66.4%) were included in the lymphadenectomy group. Overall, the authors reported a rate of lymphedema of 41.5 % among all the EC patients. Still, the comparative analysis showed that the prevalence of lymphedema was significantly higher in the lymphadenectomy cohort compared with the SLN group [49.4% (124/251) vs 26.0% (33/127); $p < 0.001$]. Furthermore, considering the patients who had only hysterectomy without retroperitoneal surgical staging, the rate of lymphedema was 27.3%. The prevalence was not statistically different from the SLN group ($p = 0.81$), suggesting that patients undergoing SLN only may have the same risk of developing lymphedema as the women who forgo intraoperative lymph node dissection and receive hysterectomy alone [32].

Geppert et al. [33] showed a significant reduction in lymphatic complications in a prospective study among EC patients who had SLN biopsy alone compared to those high-risk EC who had SLN + systematic pelvic ± para-aortic LND. Among the 181 women evaluated for lymphatic complications after a follow-up of 12 months, the incidence of LEL was significantly lower after SLN alone than after a systematic LND (1/76 patients, 1.3% vs. 15/83 patients, 18.1%; $p = 0.0003$). Moreover, the authors reported that SLN biopsy resulted in a lower incidence of pelvic lymphoceles (2/76, 2.6% vs. 11/83, 13.3%; $p = 0.02$). Of note, the assessment of LEL was performed by a specialized physiotherapist using the Common Toxicity Criteria Version 3.0 classification. Last, Accorsi et al. [34] reported the risk of LEL after SLN in a retrospective cohort study conducted in a tertiary referral center. The investigators used the MSKCC's Surgical Secondary Events Grading System to assess postoperative complications, such as LEL. No LEL (0%) was reported among the groups who had either hysterectomy only ($n = 54$) or hysterectomy plus SLN mapping ($n = 61$). Conversely, the rate of LEL was 6.7% among the overall patients who were extensively staged, hysterectomy + LND group ($n = 89$) and hysterectomy plus SLN and LND group ($n = 46$). The difference in the prevalence of LEL was statistically significant ($p < 0.01$).

## Risk factors

Several study have been conducted so far to identify risk factors associated with the development of LEL after surgery for EC.

Accumulating evidence suggests that an extensive staging surgery is associated with a higher occurrence of lymphedema than no surgical LND or SLN biopsy only [14]. Considering this point, several studies have aimed to identify the threshold of the number of removed lymph nodes associated with the risk of developing postoperative LEL. The cut-off of lymph nodes ranges

**Table 1**
Study describing the incidence of lower extremity lymphedema (LEL) after sentinel lymph node biopsy (SLN) and lymphadenectomy (LND).

| Authors, year, (ref) | Study design | Patients | LEL assessment method | Median number of nodes removed (range) | LEL incidence | p value |
|---|---|---|---|---|---|---|
| Geppert et al., 2018 [33] | Prospective study | 76 (SLN)[a]<br>83 (LND)[a,b] | CTC Version 3.0 by a specialized physiotherapist | 5 (0–18)<br>8 (0–21) | 1 (1.3%)<br>15 (18.1%) | 0.0003 |
| Accorsi et al., 2020 [34] | Retrospective cohort study | 54 (HT)<br>61 (SLN)<br>89 (LND)<br>46 (SLN + LND) | MSKCCSSEGS | NA | 0 (0%)<br>0 (0%)<br>9 (10.1%)<br>0 (0%) | 0.001 |
| Leitao et al., 2020 [31] | Retrospective cohort study | 67 (HT)<br>180 (SLN)<br>352 (LND) | 13-item LEL PRO survey | 0 (0–1)<br>4 (1–21)<br>19 (1–80) | 27 (40.3%)<br>49 (27%)<br>144 (41%) | 0.002[c] |
| Glaser et al., 2021 [32] | Retrospective cohort study | 127 (SLN)<br>251 (LND) | 13-item LEL PRO survey | 4 (3–6)<br>31(24–41) | 33 (26.0%)<br>124 (49.4%) | p < 0.001 |

**Abbreviations:** SLN, sentinel lymph node; LND, lymphadenectomy; HT, hysterectomy only; NA, not available; CTC, Common Toxicity Criteria Version 3.0 classification; MSKCCSSEGS, Memorial Sloan Lettering Cancer Center's Surgical Secondary Events Grading System; LEL, lower extremity lymphedema; PRO, patient-reported outcome.
[a] Patients with a follow-up at least of 12 months.
[b] High-risk endometrial cancer with infrarenal paraaortic and pelvic nodal staging.
[c] $p = 0.002$ using two-sample binomial proportion test comparing only SLN cohort vs LND cohort.

from 15 to 31 lymph nodes, and specifically, for each additional lymph node dissected, there is a 6% increase in the risk of developing LEL [35]. However, results of the LEG prospective study (GOG244 trial) restricted to the EC patients (n = 541), showed that patients undergoing LND with a side-specific node count >8 had an increased risk of lymphedema (OR:2.031; 95% CI 1.058–3.901, p = 0.033) [15]. Furthermore, the anatomic site of the lymph nodes removed could affect the development of LEL. Removing the circumflex iliac nodes to the distal external iliac nodes during a pelvic LND is significantly associated with higher rates of LEL [36,37]. An additional parameter to consider is the extension of surgical lymph node dissection beyond the pelvis. Yost et al. showed that the risk of LEL was not influenced by including para-aortic LND in the procedures (pelvic + para-aortic LND versus pelvic LND alone: 52.4% vs. 49.4%; p = 0.63) [30]. These findings are in line with other reports [38,39], suggesting that the extent of LND other than confined to the pelvic area may not impact the development of lymphedema.

The significant role of adjuvant treatment, such as radiotherapy or chemotherapy, on the development of LEL has been widely showed. The mechanism by which radiotherapy may play a role in the development of LEL seems to be related to decreasing the potential lymphatic proliferation and inducing interstitial fibrosis, thus leading to mechanical insufficiency, alteration of the lymphatic flow, and subsequent lymphedema [13,40]. With regard to chemotherapy, some authors concluded that this systemic therapy may increase lymph load either directly or indirectly, thereby increasing LEL risk [35].

A recent cohort study on 2493 women with lymphedema identified by a National Health Insurance Service (NHIS) database, showed that the risk of LEL was significantly increased in the group who received multimodal treatment (i.e., two or more treatment modalities). Specifically, those who received all treatment strategies (surgery + radiation therapy + chemotherapy) had the highest risk of LEL (HR 2.57, 95% CI: 2.27–2.91, p < 0.0001) [41]. However, the findings of the prospective LEG study on the LEL risk associated with adjuvant treatment were in contrast with previous data: neither adjuvant external bean radiation (p = 0.1435) nor adjuvant chemotherapy (p = 0.9692) were significantly associated with lymphedema [15]. Similarly, according to a retrospective study on 378 EC patients undergoing surgical staging in a tertiary referral center only the type of lymph node assessment (LND vs SLN) was significantly associated with the risk of LEL (OR: 2.75; 95% CI 1.69–4.47, p < 0.001), while neither adjuvant therapy nor comorbidities showed to be risk factors [32]. Thus, the identification of selected patients who need adjuvant treatment is of paramount importance also in terms of related comorbidities, and molecular classification of the tumor could help to identify patients who can forgo any further treatment [3,42].

The identification of positive lymph node has been shown to be related to postoperative lymphedema. Investigators hypothesized that the presence of tumor cells in the nodes may disrupt the lymphatic architecture, resulting in altered lymphatic drainage. However, most patients with lymph node positivity and postoperative LEL received adjuvant treatment, leaving unclear the exact association between lymphedema and lymph node metastasis [43,44].

Concerning personal characteristics, such as age, obesity, and comorbidities, the available data are contradictory: indeed, it is still unclear whether these factors truly increase the risk of LEL.

Advanced age has been suggested as a risk factor for LEL, although a clear cut-off is still not well defined [17,45]. Conversely, Carlson et al. [15] showed that advanced age was associated with a decreased risk of developing LEL (OR: 0.816; 95% CI 0.670–0.994, p = 0.0467). Obesity is a commonly reported risk factor for lymphedema, although some studies fail to demonstrate an association between a high BMI and LEL [10,17,31,35].

Lymphedema related to medical conditions is estimated to be approximately 5–6% in EC women, since the EC population is usually elderly and commonly affected by several co-morbidities [10]. On the other hand, investigators from Mayo Clinic have found that congestive heart failure was independently associated with prevalent LEL in multivariable analysis [30]. However, a clear definition of the nature of lymphedema in EC patients with comorbidities, whether related to cardio-vascular or surgery, is still challenging to understand.

Since the high rates of obesity and comorbidities among this population, potential strategies, including weight loss intervention and physical activity, could significantly impact either on reducing LEL and improve survival of these women.

## Lymphedema and impact on QoL

Survival for early-stage endometrial cancer is excellent, and treatment-associated morbidity is a crucial aspect of this cancer survivors. LEL has a negative impact to either quality of life (QoL), physical function, socialization or costs [13,31,46,47].

Recently, the GOG-244 study group confirmed that patients with symptoms of LEL were associated with poorer outcomes on QoL measures. Specifically, 768 newly diagnosed gynecologic cancer patients, including 619 EC patients, completed questionnaires measuring lymphedema symptom, QoL, body image, sexual activity, limb function, and cancer distress. The patients with symptomatic LEL reported significantly worse QoL (p < 0.001), body image (p < 0.001), sexual and vaginal function (p < 0.001), limb function (p < 0.001), and cancer distress (p < 0.001). However, the authors observed no significant differences in sexual activity rates between those with and without LLE symptoms [12].

Rowlands et al. [48] have investigated the QoL of EC patients 3–5 years after diagnosis, comparing 245 patients with LEL [n = 68 with self-reported diagnosis of LEL and n = 177 with lower limb swelling (LLS)] to women without LEL or LLS (n = 394). LLS was significantly related to reductions in both physical and mental QoL (p = 0.003 and p < 0.001, respectively).

Yost et al. [30] sought to assess the relationship between lymphedema and obesity with each scale of QoL. The authors showed that lymphedema had a greater adverse effect on QoL scores than BMI (p = 0.05), considering non-obese patients without LEL as the reference group. Indeed, the average global QoL score was 11.8 points lower in non-obese patients with LEL compared with non-obese patients without LEL, suggesting a negative role of lymphedema alone in the absence of obesity.

Recently, Dinoi et al. [49] studied the QoL in patients with EC also including those patients who are surgically staged using SLN biopsy. The study showed that obesity, LEL, and kidney disease had significant negative impacts on global QoL (p < 0.05). Additionally, the authors observed poorer global QoL scores (19.7 points lower) among morbidly obese (BMI ≥40 kg/m2) patients with LEL compared with non-obese patients without LEL.

Conversely, a recent prospective study on 97 EC patients after minimally invasive surgical staging showed that LEL was not associated with a change in global QoL. However, LEL was associated with a significant worsening lower extremity function at 4–6 weeks (−27.0% vs −3.7%, p = 0.02) and 6–9 months (−13.0% vs 0%, p = 0.01) compared to the baseline assessment [50].

Of note, an important aspect related to the LEL and QoL is the increased cancer distress reported by the EC survivors. LEL may remind the cancer experience, including stressors such as the sudden and unexpected threat of a life-altering illness, uncertainty regarding their future and the distress related to several

treatments. Future research on LEL and QoL are needed, taking into account either physical or psychological symptom burden.

## Management strategies for lymphedema

The management of LEL is extremely variable and there are no standard recommendations. However, early detection is crucial to manage lymphedema in the lower stages to avoid complications and disease progression. Management of secondary lymphedema is conservative, with surgery reserved for failed medical therapies.

Regarding conservative strategies, complete decongestive therapy (CDT) is the first option and is usually combined with physical activity. It consists of a two-step program. Phase I: characterized by skin care, manual lymphatic drainage (MLD), with or without deeper techniques including muscle pumping exercises or hydraulic pressotherapy, followed by multilayer compression bandaging aimed at improving lymphedema volume. Phase II: characterized by skincare and wearing compression garments, including low-stretch elastic stockings or sleeves. Elastic stockings or sleeves aim to prevent complications and maintain the results achieved in Phase I. Although compression should be considered the cornerstone of CDT, there is heterogeneity in the methods, timing, and duration of this treatment [51].

Another conservative option is intermittent pneumatic compression (IPC), a technique usually used in conjunction with CDT. Compression devices apply pressure gradients that increase proximally to distally to the affected limb, with pressures ranging from 80 to 110 mm Hg, pumping 4–6 h per day [52].

In addition, pharmacologic treatment of LEL is limited and mainly used to contrast local inflammatory reactions, skin fibrosis, and other complications. Medical therapy with diuretics and benzopyrones is helpful, but diuretics must be used only for short periods in patients with malignancy because they may cause electrolyte imbalance [51].

With regard to the surgical treatment of LEL, the selection of the surgical candidate is not standardized worldwide. However, surgery is indicated for those with persistent lymphedema, especially with recurrent episodes of cellulitis [53]. For patients presenting at an advanced stage with significant pitting edema, preoperative rehabilitation with CDT may be beneficial to optimize conditions for surgery. Surgical management of lymphedema consists of reconstructive (physiologic) or reductive (excisional or ablative) surgery.

Physiologic methods aim to reduce lymphatic burden by two main mechanisms: improving lymphatic circulation by transferring healthy vascularized distant tissue containing lymph nodes to the affected extremity (vascularized lymph node transfer, VLNT); and creating shunts between the congested lymphatic ducts and the venous system proximal to the site of lymphatic obstruction (lymphaticovenular anastomosis, LVA).

Lymphatic bypass surgery consists of anastomosing the lymphatic vessels or lymph nodes of the affected limb to adjacent small veins to re-establish the afferent and efferent circulation of the damaged lymphatic tissue and is effective in patients with early lymphedema. The improved lymphatic bypass surgery selects veins with good valve function, which ensures the unidirectional flow of lymphatic fluid from the lymphatic vessels into the veins and reduces the phenomenon of blood reflux and thrombus blocking the anastomosis when the pressure of the lymphatic vessels is lower than the venous pressure, thus significantly improving the long-term effect of the surgery [54].

Vascularized Lymph Node Transfer (VLNT) uses donor sites containing lymph nodes, such as the axilla or peritoneal cavity, to transplant flaps or tissues into the affected limb to re-establish lymphatic circulation in the area, effectively reducing the incidence of lymphedema and cellulitis of the lower limbs [55].

Ablative procedures should be reserved for patients with advanced LEL, fat deposition, and tissue fibrosis. These include liposuction, which requires strict compliance with compressive garments for follow-up, and direct excision, which is helpful but invasive and can cause pain, infection, healing complications, lymphatic fistulas, skin graft necrosis, and suboptimal cosmetic and functional results [56].

## Future directions and research priorities

Lymphedema is an important potential burden for survivors after surgical treatment of EC. The introduction of SLN technique enhanced a significant decrease in LEL, yielding further support for applying SLN for EC staging. However, there is no consensus regarding a standardized diagnostic evaluation tool for LEL, and the reported incidence of lymphedema differs widely among the studies.

Finally, the potential development of LEL after EC treatment may lead to reconsider the necessity of retroperitoneal lymph node dissection for all newly diagnosed early-stage cases. Indeed, in the era of precision medicine [42], the incorporation of molecular assessment for newly diagnosed EC could have the potential to influence even the surgical management of these patients. On that basis, in the near future enhanced understanding of molecular characteristics may allow the identification of a specific subgroup of EC patients with a highly indolent disease course, thereby allowing them to safely forego surgical nodal assessment. Further investigations dedicated to LEL are mandatory to generate robust evidence pertaining to this complex postoperative complication.

## Author contributions

Conceptualization, G.C.; methodology, G.C., M.C.D.; formal analysis, L.B., N.B., G. Z; writing—original draft preparation, G.C.; writing—review and editing, J.C., G.S., F.M., A.S.L.; visualization, A.S.L., A.B. supervision, V.C. All authors have read and agreed to the published version of the manuscript.

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