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Review article

Lymphedema after treatment for endometrial cancer – A review of prevalence and risk factors

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ABSTRACT

Lymphedema is one of the least studied complications of cancer treatment and a chronic condition with a substantial impact on health-related quality of life (HQoL). Lymphedema of the legs (LLL) constitutes a common adverse side effect of lymphadenectomy LA in gynecologic cancer treatment. Primary treatment of endometrial cancer (EC) comprises hysterectomy and bilateral salpingo-oophorectomy. Pelvic and para-aortic lymphadenectomy is recommended in prognostic high risk groups of EC.

This review summarizes the published literature concerning the prevalence of LLL after treatment for EC, methods used for measuring LLL, risk factors and HQoL impact.

The main findings are that the reported prevalence of LLL varies significantly between 0% and 50%. This is due to a lack of a generally accepted standardization of terminology in assessment of lymphedema. The studies use different methods to assess and grade lymphedema and often the methodology used for determining LLL is poorly described and lacks baseline measurement. Lymphadenectomy, number of lymph nodes removed, and radiation therapy seems to increase the risk for LLL. All studies dealing with HQoL show that women with LLL have impaired HQoL. The level of evidence in the published studies is generally low. Consequently it is difficult to make clear-cut conclusions about the true prevalence or determination of risk factors.

More prospective longitudinal or randomized trials with LLL as the primary outcome are necessary before conclusions can be drawn regarding prevalence of LLL and risk factor determination in EC. An internationally accepted standardization for terminology and methodology in lymphedema in research is needed.

Contents

Abbreviations: Adj., adjuvant; BMI, body mass index; BT, brachytherapy; CHT, chemotherapy; EC, endometrial cancer; GCLQ, the Gynecologic Cancer Lymphedema Questionnaire; GCLQ-K, Korean version of the Gynecologic Cancer Lymphedema Questionnaire; HQoL, health-related quality of life; ISL, International Society of Lymphology; LA, lymphadenectomy; LLL, lower limb lymphedema; LLS, lower limb swelling; LPS, laparoscopy; LPT, laparotomy; NCI-CTC, National Cancer Institute Common Toxicity Criteria; RCT, randomized controlled trial; RT, radiation therapy.

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in the developed countries. In Sweden approximately1400 women are diagnosed annually [1]. The outcome of treatment is generally favorable and the majority of patients will be long-term survivors after EC [2]. The adverse side effects of cancer treatment are therefore of importance since they can affect the health-related quality of life (HQoL) negatively and can even have negative economic effects for both the affected individual and the health care system.

Lymphedema is one of the most poorly understood, relatively underestimated, and least researched complications of cancer or its treatment [3]. Lymphadenectomy (LA) is associated with a significant risk of developing secondary lymphedema. The pathophysiology of lymphedema is complex and has been demonstrated to be not only related to proximal obstruction of the lymphatic pathways [4]. The occurrence and magnitude of lymphedema may differ substantially between individuals who have a similar extent of LA [5]; thus, it may be difficult to predict or estimate the progress and degree of lymphedema.

Studies of lymphedema of the lower limb (LLL) after treatment for gynecologic cancer where LA is performed often include various gynecologic cancers [6–10]. Women with cervical cancer are on average 25 years younger than women with EC. Consequently the results from studies on lymphedema after cervical cancer treatment can not necessarily be translated to treatment of EC. Thus it is important to determine the prevalence of LLL and its risk factors specifically in women with EC.

The risk of developing LLL after treatment for EC has received little attention although lymphedema is associated with significant HQoL impairment [11] and has been reported to cause a significant need for unmet supportive care [12].

The use of LA in EC is debated and in the American National Comprehensive Cancer Network's guidelines, surgical staging with pelvic and in high-risk tumors para-aortal LA is recommended as the primary treatment of early stage EC [13]. The Swedish national guidelines for treatment of early stage EC also recommends primary surgery with systematic pelvic and para-aortic LA in preoperatively established high risk disease (histologically endometrioid adenocarcinoma FIGO (International Federation of Gynecology and Obstetrics) grade 3, all non-endometrioid histologic subtypes, and deep myometrial invasive endometrioid tumors) but not in low risk tumors [14].

Knowledge of the prevalence and risk factors of lymphedema after treatment for EC is still incomplete. The aims of the present review study were to evaluate the prevalence of lower limb lymphedema after treatment for EC, the methods for determining the occurrence of LLL and determine the time span until onset of symptoms of LLL. In addition, we aimed to evaluate the risk factors for LLL and its impact on HQoL.

Material and methods

A search for clinical studies on lymphedema after EC treatment was performed in PubMed/Medline, Scopus, Web of Science and the Cochrane Library up to September 2016, using the search terms "*lymphedema* AND *endometrial cancer*". The search was limited to human studies published in English. The reference lists in all identified relevant articles and reviews were searched for additional published studies concerning the topic lymphedema and EC. Review articles and Cochrane Systematic Reviews which were relevant for the objective of the study, were scrutinized for references and the original articles were referred to in this study. Studies with inadequately described methods and those describing previously published results were excluded. Studies providing information about lymphedema after treatment of gynecological cancers of all sorts were included provided that they contained specific information about EC.

Results

Due to the substantial and pivotal differences in definitions and methods of measuring the outcomes it is not meaningful to enter the outcomes into a statistic meta-analysis model. Consequently the results are here presented in a descriptive meta-analysis.

Prevalence of lower limb lymphedema

The reported prevalence of LLL after treatment for EC ranged from 0% [15] up to 50% [16] (Table 1). The design of the majority of the studies giving information about the prevalence of LLL was retrospective or descriptive cross-sectional. Only two of the published articles were randomized controlled trials (RCT) but none of these were designed to evaluate LLL as the primary outcome measure. The two RCTs compared the use of LA versus no LA in surgical treatment for EC, with the primary outcomes being overall – and recurrence free survival [17,18]. In these studies the patients who had LA showed a higher prevalence of LLL, 13% and 3.5%, respectively, compared with 1.6% and 0.3%, respectively, for those without LA [17,18]. However, both studies lacked baseline information concerning leg swelling, and the method of determining the occurrence of LLL was not clearly described. One recently published prospective cohort pilot study aimed to determine the incidence of LLL using objective measurements of the lower limbs, and found that 13% of patients had LLL within two years of surgery [19]. The criteria for the diagnosis of lymphedema in that study was an increase in leg circumference of 20%.

Many of the retrospective studies were designed to compare the surgery ± LA, extent of the LA, different surgical techniques or modes of surgery in the treatment of EC. The prevalence of LLL varied considerably between these studies, from 0% [17] to 50% [16]. Besides being retrospective the common denominators for all these studies were that they might be characterized by either having no baseline data concerning leg swelling, lacked objective measures or were based on incompletely described or not validated subjective measurements. In some studies only cases with moderate to severe lymphedema or cases that complained of leg swelling and received treatment were classified as having LLL [20–22]. Consequently the true prevalence of LLL was not obtained in these studies.

In those studies where objective measurements of the LLL had been conducted the prevalence of LLL seemed to be higher than in those with subjective measures based on patient record information only. The prevalence varied from 1.2% to 28% [22,23] in the studies with subjective measurements with one exception that

Table 1
Summary of literature reporting prevalence of LLL after treatment for EC.

Authors, year, (ref), country	Study design	Patients (n)	Given treatment	Method for diagnosis of LLL	Prevalence of LLL	Risk factors for LLL
Kitchener et al. 2009 [17] UK, Poland, New Zealand, South Africa	RCT	1408	Surgery +LA 704 −LA 704 Adj. RT 33% both groups	Clinical examination but method not specifically described. Only moderate and severe cases were reported.	3.4% in + LA and 0.3% in − LA	Not investigated
Panici et al. 2008 [18] Italy	RCT	514	Surgery +LA 264 −LA 250 Adj. RT 21% Adj. CHT 7.2%	Clinical examination but method not specifically described.	LC and LLL 13% in + LA and 1.6% in − LA.	Not investigated
Hopp et al. 2015 [19] USA	Prospective longitudinal cohort study	39	Surgery +LA (100%)	Measuring the widths of the legs on three locations. More than 20% increase was defined as LLL.	13%	None (however, the study was underpowered for this purpose)
Bae et al. 2016 [40] Korea	Retrospective cross-sectional survey	154	Surgery Pelvic LA (100%) Para-aortic LA (82%) Adj. RT (28%) Adj. CHT (8.4%) Adj. RT + CHT (1.3%)	Korean version of GCLQ (GCLQ-K)	42% (lower extremity lymphedema which is described as subjective edema)	≥21 lymph nodes removed and RT
Biglia et al. 2015 [10] Switzerland	Cross-sectional survey	152 (95 EC)	Surgery (LPS 38%, LPT 62%) +LA. Adj. RT 27% Adj. RT + CHT 8.4%	Patient reports.	35% three months after surgery and 33% at time of questionnaire (≥two years after surgery).	RT and number of removed lymph nodes at three months postoperatively. No risk factors were identified two years after surgery.
Beesley et al. 2015 [39] Australia	Cross-sectional survey	1243	Surgery LA (52%) Adj. RT (29%) Adj. CHT (11%)	Medical records and postal questionnaire.	13% overall, 2.5% from questionnaire only, 7.5% from medical records and 2.9% from both sources.	Number of removed lymph nodes, ad CHT and use of non-steroid anti-inflammatory drugs (pre-diagnosis).
Hammer et al. 2014 [60] USA	Cross-sectional survey	213	Surgery (86%) Adj. RT (17%) Adj. RT + CHT (22%) Primary CHT (10%)	GCLQ	36%	Not investigated.
Salani et al. 2014 [46] USA	Cross-sectional survey	305	Surgery LA (76%)	According to patients report the diagnosis was based on physical examination (49%), measurements of lower limb (27%), no method (9%), bioimpedance measurements (3%).	22% reported clinically diagnosed with LLL, 35% reported LLS.	Not investigated.
Brown et al. 2013 [47] USA	Cross-sectional survey	213	Surgery (97%) § + RT (22%) § + CHT(17%) § + RT and CHT (10%)	GCLQ	36%	Physical activity reduced the risk of LLL for women with BMI <30.
Beesley et al. 2007 [7] Australia	Cross-sectional survey	802 (243 EC)	Surgery (98%) +LA [44] § + RT (25%) § + CHT (37%)	Validated self made questionnaire.	8.2% 14% reported undiagnosed LLS	LA and overweight or obesity.
Konno et al. 2011 [27] Japan	Retrospective case-control study	280	Surgery. +pelvic LA (49%) +pelvic and para-aortic LA (51%)	Medical records.	28% in pelvic LA 23% in pelvic and *para*-aortic LA	Not investigated.
Tanaka et al. 2007 [16] Japan	Retrospective case-control study.	184 (86 EC)	Surgery with pelvic ± para-aortic LA and ± suturing the peritoneum (46/40) Adj. RT (9.3%) Adj. CHT (26%)	Patient reports and physical examination.	25% and 50% (not sutured vs. sutured peritoneum) based on subjective symptoms. 7.2% vs. 15% when diagnosed by physician.	RT in both groups. Closed peritoneum. The positive effect regarding LLL of leaving the peritoneum open was lost if RT was given.
Hidaka et al. 2007 [20] Japan	Retrospective case-control study.	128	Surgery ± LA (68/60) 24% had both pelvic and para-aortic LA.	Medical records.	16% in the +LA group, 0% in the −LA group	LA
		77		Medical records.	0%	Not investigated.

Table 1 (*Continued*)

Authors, year, (ref), country	Study design	Patients (n)	Given treatment	Method for diagnosis of LLL	Prevalence of LLL	Risk factors for LLL
Larson et al. 1992 [15] USA	Retrospective case-control study.		Surgery ± pelvic and para-aortic LA (42/35)			
Mendivil et al. 2016 [42] USA	Retrospective cohort study	165 (135 EC)	Surgery + Pelvic LA (100%) + Para-aortic LA (31%) + RT (28%)	Medical records	3.7%	BMI >35kg/m^2 >3 co-morbidities
Mitra et al. 2016 [41] USA	Retrospective cohort study.	212	Surgery + LA (75%) Adj. RT (100%) Adj. CHT (57%)	Medical records.	7.1%	≥10 lymph nodes removed and presence of lymph node metastasis
Hareyama et al. 2015 [28] Japan	Retrospective cohort study.	358 (121 EC)	Surgery + LA (100%) Adj. CHT (60%)	Medical records.	22%	Removal of CILN, lower extremity cellulitis and number of lymph nodes removed. There was a significant reverse correlation between the prevalence of LLL and the number of lymph nodes removed.
Todo et al. 2015 [21] Japan	Retrospective cohort study.	535	Surgery + LA (100%) +Pelvic LA (49%) +Pelvic and para-aortic LA (51%) Adj. RT (5.2%) Adj. CHT (47%)	Medical records.	24%	Removal of CINDEIN; >31 lymph nodes removed and RT.
Deura et al. 2015 [6] Japan	Retrospective cohort study	126 (43 EC)	Surgery +LA (100%) Adj. CHT (37%) Adj. CHT + RT (6.3%) NAC (23%)	Objective assessment using the ISL criteria for staging. Circumference measurements (7 locations) for volume calculation.	7.0% in EC (stage 2 LLL*, stage 1 not specified for EC)	Adjuvant concurrent CHT and age ≥55 years for ≥stage 2 LLL*.
Achouri et al. 2013 [8] France	Retrospective cohort study	88 (35 EC)	Surgery + Pelvic LA (55%) + Para-aortic LA (78%) Adj. RT (23%) Adj. BT (41%) Adj. CHT (56%)	Subjective symptoms (swelling of a lower limb accompanied with pain, heaviness, erythema, or fatigability).	11%	Protective effect of postoperative drainage in univariate analysis but not in multivariate analysis.
Todo et al. 2010 [24] Japan	Retrospective cohort study.	286	Surgery +Pelvic LA (72%) +Pelvic and para-aortic LA (28%) Adj. RT (9.8%) Adj. CHT (35%)	Objective assessment using the ISL criteria for staging. Circumference measurement (7 sites) for calculating volume of the leg, MRI and/or ultrasound and lymphoscintigraphy, but data not presented.	38%	Adj. RT, ≥31 lymph nodes removed and removal of CINDEIN.
Tada et al. 2009 [23] Japan	Retrospective cohort study.	694 (301 EC)	Surgery +Pelvic LA (98%) +Para-aortic LA (22%)	Medical records and subjective symptoms.	28%	Adj. RT
Abu-Rustum et al. 2006 [22] USA	Retrospective cohort study.	1289	Surgery + LA (52%) Adj. RT (11%)	Medical records.	1.2% in total, 2.4% in + LA, 0% in – LA	LA and ≥10 lymph nodes removed.
Kodama et al. 2006 [31] Japan	Retrospective cohort study.	259	Surgery +Pelvic LA (77%) +Para-aortic LA (49%)	Medical records.	8%	Para-aortic LA was a risk factor for late postoperative complication with LLL being the most common.
Ryan et al. 2003 [9] Australia	Retrospective cohort study and interview study.	487 (141 EC). 25 EC with LLL were interviewed.	Surgery +Pelvic LA (48%) +Para-aortic LA (0,6%) +Pelvic and para-aortic LA (10%)	Subjective symptoms, definitive diagnosis by lymphedema management specialist.	18%	RT
Nunns et al. 2000 [38] Australia	Retrospective cohort study.	517	Surgery +LA (51%) Adj. RT (48%)	Medical records	4.6% in total cohort and, 9% in +LA.	Number of removed lymph nodes.
Mohan et al. 1998 [62] USA	Retrospective cohort study.	159	Surgery +Pelvic LA (100%) Adj. BT (88%) Adj. External RT (6.9%)	Medical records but method not specifically described.	5.7%	Not investigated.

Adj., adjuvant; BMI, Body mass index; BT, brachytherapy; CILN, circumflex iliac lymph nodes; CINDEIN, circumflex iliac nodes to the distal external iliac nodes; CHT, chemotherapy; EC, endometrial cancer; GCLQ; the Gynecologic Cancer Lymphedema Questionnaire; GCLQ-K, Korean version of GCLQ; LA, lymphadenectomy; LLL, lower limb lymphedema; LLS, lower limb swelling; NAC, neoadjuvant chemotherapy; RCT, randomized controlled trial; RT, radiotherapy.
*According to International Society of Lymphology (ISL) staging criteria [26]. § Not specified if given as adjuvant or neoadjuvant therapy.

showed a considerably higher prevalence (50%) [16]. In the studies with objective measurements the prevalence varied from 7.0% to 38% [6,24].

Methods for determining the LLL diagnosis

Several methods to evaluate and categorize lymphedema, e.g. American Physical Therapy Association lymphedema rating system (APTA), the Late Effects of Normal Tissue/Subjective, Objective, Management, Analytic components three item system (LENT/SOMA) and the Common Toxicity Criteria with the lymphedema criteria (CTC v2.0) have been presented but are not widely used in studies of cancer treatment. A consensus statement was presented by Cheville et al. in 2003 that recommended the use of the Common Terminology Criteria for Adverse Events (CTCAE v 3.0) in clinical trials [25]. Although the system used for the classification of lymphedema is not universally accepted, the International Society of Lymphology (ISL) issued an updated consensus statement in 2009 and 2013 regarding diagnosis and treatment of lymphedema [26]. The ISL describes four stages of lymphedema. The severity of changes within a stage may be determined by measuring the volume differences. The assessment of LLL varies widely in the published articles of EC. Still there seems to be no universally used standardization for how to measure or report LLL in scientific contexts. Table 2 summarizes the mode of assessment – subjective or objective measures – used in the published articles reviewed in this study. Only one recently published prospective study that used objective measurements of the limbs at baseline, i.e. before the cancer treatment, was identified [19]. In two Japanese studies circumferential measurements of the limbs were performed but only after the surgical treatment [6,24]. In many of the studies the assessment of LLL was based on information retrieved from the medical records or from patient reported symptoms in the survey studies. The ISL 4-grade staging of lymphedema [26] has been used by some authors [21,24,27–29], whereas others have used the National Cancer Institute Common Toxicity Criteria (NCI-CTC v2 [30]) [20,22,31,32] or the National Lymphedema Network [16] to grade the severity of lymphedema.

For the subjective scoring of LLL symptoms questionnaires have been developed in order to establish an easy assessment based on patient-self-reported symptoms (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module (EORTC-QLQ-EN24) and) Self-Report Lower-Extremity Lymphedema Screening Questionnaire in Women) [33,34]. Such a method could easily be incorporated into the clinical care setting as a simple, feasible and time-efficient screening/triaging method to identify women at a high risk of developing lymphedema. In the review of the literature, the total prevalence of LLL based on symptom specific questionnaires varied from 8.2% [7] to 47% [34]. However, in the study by Yost et al., only 17% of those who according to the questionnaire, were considered to have LLL, had previously been clinically diagnosed with LLL. This may indicate a substantial underestimation of the occurrence of LLL by simple clinical estimation [34] or an overestimation when assessing using a questionnaire only.

Risk factors for LLL

Risk factors evaluated in the studies are depicted in Table 1. LA *per se* has been shown to be an independent risk factor for LLL in several studies [7,20,22,34]. LA is not a unanimous surgical concept but differs considerably in extent of anatomical areas evacuated for lymph nodes and the number of lymph nodes removed.

The extent of LA varies from sampling of a few lymph nodes to removal of median 10–30 pelvic and/or para-aortic lymph nodes [17,18,22,35,36]. In other studies the median number of removed lymph nodes is significantly higher, up to over 80 [20,27,28,31]. The number of removed lymph nodes seems to be of importance for developing LLL with an increasing risk for LLL when a larger number of lymph nodes are removed [10,21,22,24,37–42]. Interestingly, and with no obvious reasonable pathophysiological explanation, Hareyama et al. found a significantly lower risk of LLL in women when the number of removed lymph nodes exceeded 70 [28].

The site of the lymph nodes removed may also increase the risk for LLL in gynecologic cancer. Removal of the circumflex iliac lymph nodes to the level of the distal external iliac nodes (the so called CINDEIN, also named CILN (circumflex iliac lymph nodes) or Cloquet's node) gave a significantly higher incidence of LLL [21,24,28]. The topographic extent of the LA seems to matter less. To perform both pelvic and para-aortal LA has not been shown to lead to more LLL than LA confined to the pelvic area.

The occurrence of lymph node metastases in the removed lymph nodes was shown by Mitra et al. to be a risk factor for LLL [41], but the results are contradictory [28,43].

Pelvic radiation therapy (RT) given alone or as adjuvant therapy after surgery has a varying impact on the development of LLL. In several studies RT has been shown to significantly increase the risk for LLL [9,10,16,21,23,24,34,37,40,44]. However, there are some studies that fail to demonstrate an association between RT and LLL [8,17,22]. Adjuvant chemotherapy, either given alone or in combination with RT, does not seem to have the same impact but in a few studies has been shown to increase the risk for LLL [37,39].

Overweight and obesity are associated with increased risk for EC. Therefore the populations of EC survivors may also be expected to have higher BMI than the average population. In three of the

Table 2
Mode of assessment of LLL used in articles published on treatment of EC.

Method of assessment	Reference number
Method of LLL determination not described	[15,18,35,36,49,50,52,53,55,62]
Baseline assessment performed	[19]
Objective measurement of lower limb	[6,19,24]
Using systematic clinical grading system.	
ISL	[6,21,24,27–29]
NCI-CTC	[20,22,31,32]
National Lymphedema Network	[16]
Evaluation by lymphedema management specialist	[9]
Radiology method (MRI, ultrasound)	[24,43]
Validated lymphedema specific questionnaire	[7,34,37,40,43–48,59–61]
Reported in medical record as patient complaint and/or doctors clinical evaluation	[8,16,23,38,39,41–43,51,54,58]
Subjective report from patient	[9,10,12,17,39,46]

ISL, International Society of Lymphology [26]; NCI-CTC, National Cancer Institute-Common Toxicity Criteria [30].

descriptive studies where the participants answered a questionnaire concerning LLL, higher BMI was significantly associated with more LLL symptoms [34,42,44,45] while in other studies such an association between BMI and risk for LLL was not demonstrated [8,24,28,41,46].

Higher levels of physical activity have been associated with a significantly reduced risk for LLL. In the study by Brown et al. [47] a higher level of physical activity was a preventive factor for LLL but only among women with BMI $<30\ kg/m^2$.

Age has also been associated with the development of LLL in gynecological cancer but the results are contradictory. Deura et al. [6] found age over 55 years to be an independent risk factor for LLL. Ferrandina et al. showed that women over 60 years had a higher risk for LLL but only in a univariate analysis [48]. Several studies have shown no such association between age and risk for development of LLL [22,24,28,40,41,46]. Thus, it remains unclear whether BMI or age truly are risk factors for LLL in EC patients.

In the large retrospective review by Abu-Rustum et al. including 1289 patients, 5.7% reported swelling of the legs due to other medical conditions [22]. Survivors of EC as a population are likely to be older and to have higher BMI, resulting in more co-morbidity including being at risk for other medical conditions which may give symptomatic swelling of the legs. Yost et al. [34] found that congestive heart failure was an independent risk factor for LLL. The diagnosis was based on a self-reported screening questionnaire. Whether this finding reflected a true increased risk of LLL or simply a swelling of the legs on the basis of cardio-vascular disease was not evaluated.

A summary of the studies on mode of surgery for EC and LLL is shown in Table 3. Minimal invasive surgery is considered theoretically to decrease the risk of developing LLL. However, this remains to be proven. In a prospective study, women with EC were randomized to laparoscopic surgery (LPS) or laparotomy (LPT). In the LPT group, 3.4% developed LLL compared with none in the LPS group [49]. However, the study gave no information on how the LLL diagnosis was obtained. Several retrospective studies have compared LPS to LPT in EC and in some cases also robot-assisted LPS. The reported incidence of LLL vary from 0.9% [36] to 1.6% [49] with a higher incidence after LPS in two of the studies [35,50]. Another study showed no difference between the groups at all [51]. Two studies compared LPT, LPS and robot-assisted LPS [36,52]. However, only one patient were diagnosed with LLL in each of these two studies; one in the LPT group in [36], and one in the robot-assisted LPS group in [52]. When comparing conventional LPS with robot-assisted LPS no difference in prevalence of LLL was found, 2% and 3%, respectively [53]. In four studies with only robotic surgery comprising pelvic and/or para-aortic LA [29,32,54,55], the LLL incidence was reported to be 5.2% to 21%, with a lower incidence, although not statistically significant, when the operation had been converted to LPT [54]. In all of these studies the diagnosis of LLL was based on information from the medical records, with no systematical measurements performed except in the study by Geppert et al. [32] who used the NCI-CTC classification prospectively on those with symptomatic LLL but without baseline evaluation.

Closure of the pelvic peritoneum at surgery may be a risk factor for developing LLL [16,28]. The risk of developing LLL decreased by nearly 50% if the pelvic peritoneum was left open [16]. Hareyama et al. found a statistically significant association between closure of the peritoneum and occurrence of LLL with a more than 4-fold higher prevalence of LLL if the peritoneum was closed (28.3% vs. 7.9%) [28].

Other risk factors are associated with lymphedema, such as lower extremity cellulitis, but this condition was only reported as a risk factor in the study by Hareyama et al. [28].

Follow-up time and onset of symptoms of LLL

LLL is considered to be a chronic disease [24,56] and progressive if untreated [57]. There is large variation in follow-up periods in the published studies. In women treated for gynecologic malignancy, 75% developed LLL within the first year after diagnosis of cancer. In 19% of the patients, LLL was diagnosed between one and two years, and 6% of patients developed LLL between two and five years after cancer diagnosis [7]. In EC 32% developed symptoms of LLL within four weeks after surgery [46]. Within one year after surgery for gynecological cancer it seems that the majority of cases with symptomatic LLL have been developed [7,9]. Lymphedema onset may begin immediately after surgery or may be delayed for many years [41,58]. Long-term follow-up is therefore essential in order to establish reliable results on time of onset of LLL. An Italian prospective longitudinal study evaluated HQoL in EC, using questionnaires including symptoms of LLL, at baseline and follow-up at three, six, 12 and 24 months after surgery. The highest levels of LLL-symptom scores were found six months postoperatively with a trend to recover at 12 and 24 months postoperatively [48].

It seems that LLL after adjuvant radiotherapy may even show a trend for improvement over time. Mitra et al. found in a retrospective study that median time to onset of LLL was eight months, and more than 50% of LLL improved or resolved within 10 months without a clear association with documented interventions to treat the LLL [41].

Impact on HQoL

Table 4 summarizes the studies of HQoL and LLL in EC. An analysis of the HQoL three to five years after treatment of EC showed significantly lower HQoL in those with LLL, with the lowest score on physical functioning [37]. In a comparison of HQoL between a group without LA, and EC survivors who had undergone surgery including pelvic and para-aortal LA, symptoms indicating LLL were the only dimension that differed significantly between the groups with a higher score in the LA group. However in that study, the global health status score was equal in the two groups [59]. In women experiencing physical and functional impairment after surgery for uterine cancer, with LLL being the most common impairment, the level of physical activity was found to be significantly reduced [60]. Among women treated for EC those with LLL were more likely to report unmet supportive care needs [12].

Radiotherapy in the treatment of EC seems to be a risk factor for LLL and consequently it would be likely to affect HQoL. A large retrospective Dutch study investigated the impact of LA with and without adjuvant RT on HQoL but found no clinically relevant differences in overall HQoL between the groups [61]. Karabuga et al. showed negative effect on HQoL after external RT and vaginal brachytherapy with significantly more LLL symptoms after external RT [44].

Comments

The true prevalence of LLL after treatment of EC remains to be established. The great variety in the reported prevalence of LLL reflects the lack of standardization of terminology and ways of measuring LLL in research and use of inadequate methodology. Initially, the purpose of this study was to perform a systematic review with a meta-analysis of the studies included but due to the large and pivotal differences in methodology regarding measuring lymphedema and the lack of objective and uniform definition of the disease the results of the studies are not, in most cases, comparable with each other. Consequently, a statistical meta-

Table 3
Summary of studies on impact of mode of surgery for EC on development of LLL.

Author, year, (ref. nr.), country	Study design	Patients (n)	Primary outcomes	Prevalence of LLL	Method for diagnosis of LLL	Main findings
Geppert et al. 2015 [32] Sweden	Prospective longitudinal cohort study.	140	Feasibility and incidence of lymphatic complications of robotic surgery with pelvic and para-aortic LA for EC.	14%	Physical examination. LLL was graded after NCI-CTC v. 3.0.	Infrarenal para-aortic LA by robotic surgery was feasible in 70% of high risk EC.
Tozzi et al. 2005 [49] Germany	Prospective randomized trial.	122	To compare LPS (n = 63) and LPT (n = 59) for intra- and postoperative complications	1.6% in total. 3.4% LPT 0% LPS.	Medical records	Significant lower incidence of late postoperative complication in the LPS group.
Herling et al. 2015 [29] Denmark	Retrospective cohort study	235	Surgical complications after robotic surgery ± pelvic LA.	21% in the group with LA, not specified in the other group.	Medical records based on physical examination. LLL was graded according to ILS grading system.	No significant difference between the groups in incidence of overall complications.
James et al. 2014 [55] USA	Retrospective cohort study.	97	Clinical performance of robotic surgery with infrarenal LA.	5.2%	Medical records	Infrarenal LA was possible in 95% with BMI<35 and in 81% with BMI >35.
Ghezzi et al. 2012 [51] Italy	Retrospective cohort study	261	Incidence of LLL, lymphoceles and lymphorrhea after surgery including pelvic LA by LPS (n = 138) or LPT (n = 123) for EC.	14% in total. 13% in LPS 15% in LPT	Medical records, based on physical examination or patients reported symptoms.	No difference between the groups in prevalence of LLL. Significantly lower prevalence of lymphoceles in the LPS group.
Backes et al. 2012 [54] USA	Retrospective cohort study	503	Surgical complications and postoperative morbidity after robotic surgery for EC.	13%	Medical records	Robotic surgery for EC had a low risk of short-term complication and LLL was the most common long-term morbidity. 86% of LLL cases were classified as mild or moderate.
Barnett et al. 2011 [50] USA	Retrospective case-control study	376	To compare adverse event rates after LPS (n = 107) and LPT (n = 269) for EC.	In total 2.9%. 7.5% in LPS 1.1% in LPT With LA: 11% respective 1.6%.	Medical records	LPS gave higher incidence of LLL and peripheral sensory nerve deficit but lower incidence of wound infection than LPT.
Bell et al. 2008 [36] USA	Retrospective case-control study	110	To compare operative and peri-operative outcomes, complications, adequacy of staging and costs for LPT (n = 40), LPS (n = 30) and robot assisted LPS (n = 40) for EC.	0.9% in total 2.5% in LPT (1 patient) and 0% in LPS and robot assisted LPS.	Medical records	Robotic surgery was associated with lower postoperative morbidity but longer operating time. Costs were highest for LPT and lowest for LPS. The number of retrieved lymph nodes was comparable in the groups.
Boggess et al. 2008 [52] USA	Retrospective Case-control study	322	To compare outcomes after endometrial staging by three surgical techniques (LPT (n = 138), LPS (n = 81) and robot assisted LPS (n = 103)).	0.3% in total 1.0% in robot LPS group (1 patient)	Medical records	Robotic surgery was associated with significantly shorter operating time, less blood loss, shorter hospital stay, fewer postoperative complications and higher number of retrieved lymph nodes) compared with LPT.
Gehrig et al. 2008 [53] USA	Retrospective case-control study	160	To compare peri- and postoperative results for robotic surgery (n = 79) with standard LPS (n = 81).	3,0% in robotic LPS 2.0% in LPS (both groups including LLL and lymphocyst).	Medical records	Robotic surgery was associated with significant shorter operating time, less blood loss, shorter hospital stay and increased number of retrieved lymph nodes.
Kuoppala et al. 2004 [35] Finland	Retrospective case-control study	80	To compare efficacy, safety and complications between LPS (n = 40) and LPT (n = 40) for EC.	10% in total. 13% in LPS and 7.5% in LPT.	Medical records	Similar outcome in both groups. LLL and pelvic lymph cysts were the most frequent late postoperative complications. LPS gave faster recovery and fewer wound infections but longer operating time.

EC = endometrial carcinoma, LA = Lymphadenectomy, LLL = lower limb lymphedema, LPS = laparoscopy, LPT = laparotomy; NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

analysis is not meaningful and we therefore present the review as a descriptive meta-analysis.

The vast majority of the published studies lack baseline measuring of limbs or symptom scoring and are not designed to measure LLL as the primary outcome. Often the diagnosis is based on clinical evaluation of women subjectively complaining of swollen legs, or on the answer to symptom-specific questions in questionnaires. With a solely subjective assessment of symptoms, other causes of swelling are at risk of being overlooked or incorrectly taken for lymphedema. Consequently, the prevalence of LLL may be overestimated in such studies.

The ISL grading recommendation is rarely used in the published articles. Many of the retrospective studies are chart reviews. If standardization for assessing LLL is lacking there is an apparent risk that mild and moderate edemas may be overlooked and consequently the prevalence of LLL may be underestimated. It is obvious that swelling legs may easily be interpreted as LLL when lymphadenectomy has been conducted, but other reasons for

Table 4
Summary of studies on HQoL with EC and LLL.

Author, year, (ref. nr), country	Study design/methods	Patients (n)	Primary outcome	Main findings
Ferrandina et al. 2014 [48] Italy	Prospective. Baseline questionnaire (EORTC QLQ-C30, EORTC QLQ-CX24 and HADS) at diagnosis (before consultation about treatment). Questionnaires were then answered at 3,6,12 and 24 months postoperatively.	134 were enrolled and 94 completed	HQoL and emotional distress in EC patients.	LLL- and menopausal symptoms heavily affect HQoL in EC patients. The LLL-scores worsened over time with highest levels at 6 month with a trend to recover at 12 and 24 months.
Rowlands et al. 2015 [12] Australia	Cross-sectional survey study. Questionnaires (CaSUN, FACT-EN, HADS) were answered at diagnosis and after 3–5 years	629 (response rate 50%)	Prevalence of unmet needs 3–5 years after treatment for EC.	24% reported one or more unmet supportive care needs in the last month. 11% were diagnosed with LLL, 27% reported LLS. Both LLL and LLS were associated with having unmet needs.
Kim et al. 2015 [43] Korea	Cross-sectional case-control survey study. HQoL questionnaires (EORTC QLQ-C30 and GCLQ-K) were used. Diagnosis of LLL was made by physical examination and various limb measurement methods (perometry, lymphoscintigraphy, MRI, CT).	53 (11 EC). (25 with and 28 without LLL)	To evaluate the impact of LLL on HQoL in gynecologic cancer patients after pelvic LA.	Women with LLL had significantly higher symptom scores in the GCLQ-K and reported an impact on financial situation. The global health status was not significantly affected by the LLL diagnosis.
Karabuga et al. 2015 [44] Turkey	Cross-sectional survey study. Two HQoL questionnaires were used (EORTC QLQ-C30, CX24).	144	HQoL and sexual function in EC patients who received Adj. RT (Adj. external RT and/or adj. vaginal BT).	Adj. external RT had a negative effect on HQoL compared with adj. vaginal BT. After ad external RT LLL symptom scores were significantly higher. BMI >30 was associated with more LLL symptoms.
Rowlands et al. 2014 [37] Australia	Cross-sectional survey study. Telephone interview with nurse at diagnosis, and a questionnaire (SF-12) 3–5 years later.	639 (response rate 50%)	To assess and compare HQoL of women with LLL (self-reported), LLS and those without LLL or LLS after treatment for EC.	11% reported diagnosed with LLL, 28% reported LLS. > FIGO stage I at diagnosis, >15 lymph nodes removed and adjuvant RT and/or CHT were risk factors for LLL. Women with LLL scored significantly lower on overall physical HQoL with the lowest score on the physical functioning subscale.
Yost et al. 2014 [34] USA	Cross-sectional survey study. A LLL screening questionnaire (self-made) and two HQoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-CX24) were answered.	591 (response rate 56%)	Prevalence of LLL after surgery for EC, and to identify predictors of LLL and evaluate the effect of LLL on HQoL.	17% reported being previously diagnosed with LLL and another 30% were diagnosed with LLL according to the questionnaire, total prevalence 47%. 36% with LLL after hysterectomy and 52%.,when LA was conducted Higher BMI, congestive heart failure, LA and RT were associated with LLL. Multiple HQoL scores were worse in women with LLL regardless of BMI. Women with BMI >40 and LLL had the lowest HQoL scores.
Angioli et al. 2013 [59] Italy	Cross-sectional survey study. Two HQoL questionnaires (EORTC QLQ-C30, EORTC QLQ-EN24) were answered.	76 (response rate 80%). 40 + LA, 36 − LA	HQoL after surgery for EC ± LA	LLL symptoms were the only symptoms that were significantly different between the groups. The global health status was unaffected.
Oldenburg et al. 2013 [45] The Netherlands	Cross-sectional survey study. (SF-36 and EORTC QLQ-EN24 were used)	666 (response rate 77%).	To assess the association between BMI and HQoL after treatment of EC.	BMI was related to several HQoL outcomes. Those with higher BMI had more LLL symptoms. Women with BMI ≥35 had a 8.5 points higher score for LLL symptoms than normal weight women (adjusted for treatment). BMI was self-reported.
van de Poll-Franse et al. 2012 [61] The Netherlands	Cross-sectional survey study. (SF-36, EORTC QLQ-EN24 was used)	742 (response rate 77%)	HQoL after treatment for EC with pelvic LA but no RT compared with no LA but RT in the presence of risk factors.	After LA the LLL symptom scores were significantly higher. The group with RT had more gastro-intestinal symptoms. Overall no difference in HQoL was found between the groups.

Adj., adjuvant; BMI, body mass index; BT, brachytherapy; CaSUN, Cancer survivors' unmet needs measure; CHT, chemotherapy; CX24, Cervical Cancer Module (the supplemental 24-item module to EORTC QLQ); CT, computed tomography; EC, endometrial carcinoma; GCLQ-K, Korean version of the Gynecologic Cancer Lymphedema Questionnaire; EORTC QLQ-C30/EN24, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, 30 and 24 items questionnaire, respectively; FACT-EN, the Functional Assessment of Cancer Therapy – Endometrial Cancer Subscale; HADS, Hospital Anxiety and Depression Scale; HQoL, Health-related Quality of Life; LA, lymphadenectomy; LLL, lower limb lymphedema; LLS, lower limb swelling; MRI, magnetic resonance imaging; RT, radiotherapy; SF-12/SF-36, Short Form Health Survey, 12 and 36-Items version, respectively.

swelling legs must be ruled out in this population of elderly EC survivor women.

Lymphedema is a chronic, progressive condition, often leading to disability if untreated or under-treated. Established lymphedema is a serious condition which may be lethal. Septic shock and lymphangiosarcoma are known complications to lymphedema. Therefore it is important to prevent the development of lymphedema. Treatment in early stage is important in order to reduce the severe long term effects and even mortality. The published studies in this review lack detailed information about treatment of LLL.

Although there seem to be several potential risk factors for LLL in EC the determination of risk factors still remains to be evaluated in correctly designed trials with appropriate standardized

methodology for determining LLL in order to establish the risk factors. However, three conditions – lymphadenectomy [7,11,22,34], number of removed lymph nodes [10,21,22,24,37–42] and radiation therapy [10,16,21,23,24,34,37,40] – appear to present the strongest evidence for a causal association. From the current literature no conclusion can be made about the impact of mode of surgery and the risk of developing LLL in EC.

LLL is a chronic condition and many women experience substantial negative physical and psychological effects on daily living as indicated almost unanimously in the results of HQoL studies in the literature concerning EC.

There are some limitations to be concerned in this review. The search was limited to studies published in English. However, the reference lists in all identified relevant articles and reviews were searched for additional published studies concerning the topic lymphedema and EC and consequently important studies published in non-English languished journals would reasonably have been identified. Another limitation is the risk of reporting bias which is constantly present in review articles and its possible impact on the outcome measures of this review might be difficult to estimate.

In conclusion, this review exposes essential weaknesses and the lack of high grade evidence in the comprehensive knowledge of lymphedema after treatment of endometrial cancer. An internationally accepted standardization for terminology and methodology in lymphedema in research is needed. We suggest and encourage the international scientific societies who deal with lymphedema to assemble and agree on these issues making evidence based international guidelines of methodology for diagnosis and treatment recommendations. Research with a focus on LLL as the primary outcome measure in well-designed prospective long-term follow-up trials with structured assessments using validated objective measurements and information about patient reported experience/outcome measures (HQoL) is needed in order to establish valid data on prevalence, time of onset of lymphedema development and risk factors for LLL after treatment for EC.

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Conflicts of interest

None of the authors have conflicts of interest to declare.

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