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Review

A Reappraisal of Lymphadenectomy in Common Gynecological Cancers

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Abstract

Objectives: Lymph node dissection (LND) in gynecological malignancies has always been a cornerstone in the diagnosis of metastasis, it is also considered an important prognostic factor, and a reliable guide to management strategies. However, its incidence of complications, namely lymphedema, vascular injuries and other lesions, has led to a reconsideration of its efficacy and a comparison of the role of systematic *vs*. sentinel lymph node (SLN) dissection. **Mechanism**: Review of the literature using keywords such as "lymph nodes", "sentinel lymph nodes", "morbidity and mortality", "gynecological cancers", "endometrial cancer", "ovarian cancer", and "cervical cancer". **Findings in Brief**: In the case of endometrial cancer, several studies have investigated the efficacy of SLN compared with systematic LND. Most of the results demonstrated the efficacy of SLN dissection in endometrial cancer, with the added benefit of lower morbidity. In patients with ovarian cancer, the mainstay of treatment is debulking with optimal cytoreductive surgery. Recent studies have compared systematic lymphadenectomy to non-lymphadenectomy, with an additional advantage in the cases of lymphadenectomy. However, since its publication, the lymphadenectomy in ovarian cancers (LIONS) trial, has revolutionized the standard of care for patients with advanced ovarian cancer and has called into question the increased morbidity and mortality in systematic lymphadenectomy. In cervical cancers, lymph node status is considered to be the most important prognostic factor. In this case, limiting lymphadenectomy to the borders of the inferior mesenteric artery seems promising, and studies are currently being carried out to investigate the feasibility of SLN dissection instead of systematic lymph node dissection. **Conclusions**: SLN dissection is associated with lower morbidity and mortality, and has been shown to be superior to systematic lymphadenectomy in several studies. However, more research and specific guidelines are needed to better select either one or the other method in the management of gynecological cancers.

Keywords: lymph nodes; sentinel lymph nodes; morbidity and mortality; gynecological cancers; endometrial cancer; ovarian cancer; cervical cancer

1. Background

Lymph node dissection (LND) is a cornerstone of the diagnosis of cancer and its metastasis in gynecological malignancies. Gynecological cancer usually spreads via the lymphatic system, which is considered to be the main route of dissemination. Therefore, LND is a common procedure for assessing extension, and is an important prognostic factor, which strongly influences adjuvant treatment decisions. However, the morbidity associated with systematic LND has led to its reconsideration in the field of oncology, with research currently investigating the efficacy of systematic *vs*. sentinel lymph node (SLN) dissection [1].

The morbidity of this procedure, similar to other surgeries, is increased in the elderly, the obese and patients with cardiovascular risk factors [1]. In addition to the surgical risks, which mainly include vascular injuries, postoperative lymphedema has been described as the most frequent complication [1]. Yost *et al*. [2] revealed that lymphedema is associated with LND, with a 23% increase in risk compared with simple total hysterectomy. In another study conducted by Beesley *et al*. [3], where 1243 patients treated for endometrial cancer were included, the incidence of lymphedema was 13%, particularly prevalent in patients who had more than 15 lymph nodes removed intra-operatively. Adjuvant radiation, chemotherapy and use of non steroidal anti-inflammatory drugs have been shown to be risk factors for lymphedema. However, the reason for these associated risk factors has not yet been found. Achouri *et al*. [4] reported that the occurrence of lymphocele has also been described after LND in gynecological malignancies, with

an incidence ranging from 0 to 58.8%. Increased operative time, blood loss and longer hospitalization has also been reported as co-morbidities associated with LND [5].

An equal risk has been observed in terms to febrile morbidity, transfusion rate and post-operative mortality [5]. With the advancement in minimally invasive surgery and its widespread use, surgical morbidity has been considerably reduced [6]. Benito *et al*. [7] conducted a study of 444 cases of lymphadenectomy, which confirmed the safety and feasibility of the procedure despite a complication rate of 1.9%, such as bowel, ureter or vascular injuries.

A less morbid alternative has since then been studied: SLN dissection and its various techniques [1]. SLN dissection was first described by Gould *et al*. [8] in 1960 while studying parotid gland cancers. SLN represent the lymph node(s) most likely to be affected by the metastatic disease. This technique was first applied to the early stages of melanoma and breast cancer. Afterwards, its application gained wide interest in gynecological malignancies [6]. Studies have shown that SLN reduce surgical radicality, thereby reducing morbidity and allowing better detecting lymph node metastases [6]. Recent evidence showed an improvement in the detection of early-stage metastasis using SLN assessment, due to its accuracy in identifying by coloration the first lymph node to harbor cancer in case it exists [6].

In this paper, a literature review has been conducted to discuss lymphadenectomy procedures and their implication in gynecological pelvic malignancies.

2. Endometrial Cancer

2.1 Endometrial Cancer and Lymph Node Dissection

Since 1985, total hysterectomy with bilateral salpingoophorectomy and complete surgical staging by LND has been the recommended standard of care for endometrial cancer [9]. The incorporation of LND had an additional benefit of identifying patients with nodal dissemination who may benefit from adjuvant therapy, and helped eliminate metastatic disease which could have been disregarded with hysterectomy alone [6]. A higher survival rate has been detected in patients who underwent systematic LND for endometrial cancer, compared to conventional surgical treatment, i.e., total hysterectomy with bilateral salpingoophorectomy, peritoneal washings and lymph nodes palpation.

It has been emphasized that endometrial cancer with metastatic lymph nodes is associated with a poor prognosis that would certainly need adjuvant radio and chemotherapy [10]. Endometrial cancer usually metastasizes to the pelvic, and later on to para-aortic lymph nodes. The MRC ASTEC Trial conducted by Kitchener *et al*. [11], and the randomized clinical trial conducted by Benedetti *et al*. [12], revealed that overall survival rate of endometrial cancer is independent of lymph node dissection, and depends instead on the effect of adjuvant therapy. Thus, sentinel pelvic lymph node biopsy is now considered as a valid alternative with fewer morbidities, while retaining the same value of nodal assessment [13]. In other words, SLN assessment is a mere reflection of the overall pelvic pathology, while avoiding nearby organs, lymphedema, and increased operating time and blood loss.

According to Taran *et al*. [14], several techniques and injection sites have been described for SLN dissection. These include cervical injection sites, injection into the uterine fundus or hysteroscopic guided peritumoral injection into the endometrium [14]. The products of injection include dyes (such as indocyanine green, methylene blue, patent blue and others) as well as radioactive tracers (Tc99m) [15]. A study conducted by Rossi *et al*. [16] showed that cervical injection of dyes is more consistent than hysteroscopic guided injection for overall detection rates.

2.2 Lymph Node Dissection and Early-Stage Endometrial Cancer

Performing systematic LND in women with endometrial cancer could lead to “overstaging”, as most patients with endometrial cancer present it at an early clinical stage [17]. However, controversy still persists over LND in early-stage endometrial cancer [6]. Several algorithms have been developed to identify patients for whom LND dissection is not necessary, the most commonly used one is the “Mayo Algorithm” [18,19]. The Mayo algorithm initially introduced in 2000, was validated in 2011. It exempts patients with Federation International of Gynecology and Obstetrics (FIGO) grade 1 and 2 tumors of endometrioid histology from full staging [20]. However, although the Mayo Algorithm in increasingly used, studies conducted by Leitao *et al*. [21] and by Frumovitz *et al*. [22] question the reliance on preoperative pathology and frozen section results to classify patients as requiring LND or not.

Tschernichovsky *et al*. [1] carried out a literature review to study the feasibility, diagnostic accuracy, and oncologic outcomes of SLN biopsy in early-stage endometrial cancer compared to systematic lymphadenectomy. Most series showed a high diagnostic rate and a low false negative rate for SLN biopsy. Furthermore, SLN biopsy was not inferior to lymphadenectomy in terms of disease-free survival and overall survival [1]. It was finally concluded that SLN biopsy in addition to being less morbid, is considered to be a more accurate alternative to systematic lymphadenectomy in early-stage endometrial cancer [1].

In the case of early-stage endometrial cancer, systematic LND is usually recommended in high-risk patients, and is usually avoided in low-risk patients. To re-evaluate this risk-stratified strategy, Pölcher *et al*. [23] conducted a population-based study on 5546 patients using data extracted from the Munich Cancer registry. No difference was found between patients with and without LND in the following outcomes: time to local recurrence, lymph node

recurrence and distant metastasis, among the different risk-stratified groups [23]. It has therefore been concluded that in early-stage endometrial cancer, systematic LND does not provide any additional overall benefit in terms of overall survival. Furthermore, it is not reliable to use a risk-stratified strategy to allocate patients to lymphadenectomy *vs*. non-lymphadenectomy [23].

A multicenter prospective cohort study was conducted by Cusimano *et al*. [13], to study the diagnostic accuracy, performance, and morbidity of SLN in patients with intermediate and high-grade endometrial cancer. A total of 156 patients were recruited, out of which 126 had high-grade endometrial cancer. Results revealed that SLN detection rate was 97.4%, from which 87.5% were hemipelvic lymph node dissection [13]. SLN dissection correctly identified 26 out of 27 patients in this later study, with a sensitivity level of 96% (95% confidence interval (CI)), a false negative rate of 4% (95% CI), and a negative predictive value of 99% (95% CI) [13]. These results reiterate that SLN biopsy has high diagnostic accuracy for patients with endometrial cancer compared with lymphadenectomy. SLN dissection is therefore a reliable alternative for surgical staging of endometrial cancer [13].

The (Fluorescent Imaging for Robotic Endometrial Cancer Sentinel lymph node biopsy) (FIRES) trial, a multicenter prospective cohort study was conducted by Rossi *et al*. [24] across the United States of America whereby 18 surgeons from 10 different centers took part in this study. Its aim was to identify the sensitivity and negative predictive value of SLN biopsy in patients with metastatic endometrial cancer, compared to systematic lymphadenectomy. A total of 375 patients with endometrial cancer of all histological types and all grades undergoing robotic staging were included in this study. The results revealed that SLN mapping can accurately detect metastatic disease with a sensitivity level of 97.2% and a negative predictive value of 99.6%. It was therefore concluded that SLN mapping has a high diagnostic accuracy in detecting metastatic endometrial cancer, with the added benefit of avoiding the morbidity associated with lymphadenectomy [24].

Yu *et al*. [25] published a review aiming to study the feasibility of SLN biopsy in high-grade tumors, as most of the previously published data was based on low-grade tumors. In their review, studies suggested that the application of SLN mapping for high-grade endometrial cancers is feasible and practical, as it was shown to have a high detection rate with a sufficiently low negative predictive value. However, it was concluded that SLN mapping has to follow a well-revised algorithm, and that the surgeon's expertise is a very important prognostic factor in these cases [25].

Table 1 (Ref. [1,11–13,23–25]) is a summary of the main results for endometrial cancer.

2.3 Ovarian Cancer and Lymph Node Dissection

Standard treatment for advanced epithelial ovarian carcinomas includes debulking surgery and taxane- and platinum-based chemotherapies [26]. Maximal efforts at cytoreductive surgery have been supported to reduce residual disease [27]. However, systematic lymphadenectomy in patients with advance ovarian cancer remains controversial [28]. Retrospective studies conducted by Chen *et al*. [29] and Scarabelli *et al*. [30], found better survival rate in patients undergoing systematic lymphadenectomy for advanced stage ovarian cancer. Panici *et al*. [28] conducted a multicenter randomized controlled trial to study the progression-free and overall survival rate of systematic aortic and pelvic lymphadenectomy in women with advanced ovarian cancer. Their results showed that progression-free survival rate was improved in systematic lymphadenectomy cases; however, overall survival rate was similar in both arms [28]. This study conducted as part of a multicenter, randomized clinical trial demonstrated that systematic lymphadenectomy is feasible. Intraoperative and postoperative complications were higher in women who underwent lymphadenectomy, yet, these complications were mild, including lymphocele or lymphoedema, longer operating time and slightly higher estimated blood loss [28]. Several observational studies have been conducted to compare the survival rate in patients undergoing cytoreductive surgery and lymphadenectomy to patients undergoing cytoreductive surgery alone. All these studies favored lymphadenectomy, which was found to have better survival rate [29,31–33].

In stage IIIC and IV ovarian cancer, the role of systematic LND remains controversial as this procedure has no effect on the surgical stage and its therapeutic benefit is still uncertain [28,30,34]. Current National Comprehensive Cancer Network (NCCN) guidelines recommend the removal of suspicious and/or enlarged nodes in patients with advanced disease, rather than systematic LND [26]. Systematic LND for advanced ovarian disease requires further studies in the era of radical surgery [26].

Several retrospective and prospective trials have been conducted to study the influence of systematic *vs*. non-systematic lymphadenectomy in ovarian cancer. The lymphadenectomy in ovarian neoplasms (LION) trial, was a prospectively randomized trial conducted to study the effect of lymphadenectomy in 647 patients who underwent neoadjuvant chemotherapy in advanced ovarian cancer [35]. There was a difference in median overall survival rate with an average of 3.7 months additional survival in the non-lymphadenectomy group [36]. However, there was no difference in the progression-free survival rate with an average of 25.5 months. In terms of post operative complications, there was a statistically significant difference, with a 12.4% complication rate in the lymphadenectomy group compared with only 6.5% in the non-lymphadenectomy group [36]. Similarly, mortality in the 2 months following-surgery was 3.1% compared with 0.9% in the non-lymphadenectomy group [36]. Since its publication, the LIONs trial has revolutionized the standard of care for patients with advanced

Table 1. Summary of main results for endometrial cancer.

Authors	Type	Patients	Conclusion
Kitchener *et al*. [11]	Randomized clinical trial	1408 women with histologically proven endometrial carcinoma Standard surgery *vs*. Standard surgery plus lymphadenectomy	No evidence of benefit in terms of overall or recurrence-free survival for pelvic Lymphadenectomy
Benedetti *et al*. [12]	Phase 3 randomized trial	Pelvic systematic lymphadenectomy (n = 264) or no lymphadenectomy (n = 250) in early-stage endometrial carcinoma	Systematic pelvic lymphadenectomy statistically significantly improved surgical staging, it did not improve disease-free or overall survival
Tschernichovsky *et al*. [1]	Literature review	-	In some series, the reported detection rates of sentinel lymph node have reached upward of 90%, with false-negative rates as low as 0%
Pölcher *et al*. [23]	Population based study	5546 patients	Sentinel lymph node does not provide additional benefit in terms of overall survival
Cusimano *et al*. [13]	Prospective multicenter cohort study	126 patients with high-grade endometrial cancer Sentinel lymph node biopsy *vs*. Lymphadenectomy (Pelvic lymph node dissection)	Sentinel lymph node detection: 97.4% (Sentinel lymph node) *vs*. 87.5% (pelvic lymph node dissection) Se: 96% False negative rate 4% Negative predictive value 99%
Rossi *et al*. [24]	Multicenter prospective cohort	385 patients with clinical stage 1 endometrial cancer. All grades and histological type Robotic staging	Sentinel lymph node metastatic disease detection 97% Se 97.2% Negative predictive value 99.6%
Yu *et al*. [25]	Review	High-grade endometrial cancer	High rate of SLN detection

SLN, sentinel lymph node.

Table 2. Summary of main results for ovarian cancer.

Article	Type	Patients	Conclusion
Chen *et al*. [29]	Prospective study	75 patients with epithelial ovarian carcinoma all stages	Better survival rate in patients with systematic lymphadenectomy
Scarabelli *et al*. [30]	Case control study	105 patients with advanced or persistent epithelial ovarian cancer. Lymphadenectomy *vs*. non-lymphadenectomy	Systematic lymphadenectomy improved survival in previously untreated patients
Panici *et al*. [28]	Multicenter randomized controlled trial	427 patients. Histologically proven and optimally debulked epithelial ovarian carcinoma with Federation International of Gynecologists and Obstetricians stages IIIB and IIIC Stage IV patients were eligible if the only evidence of stage IV disease was malignant cells in pleural effusion	Progression free rate 56.3 months (no-lymphadenectomy) *vs*. 62.1 months (lymphadenectomy) median overall survival rate: 56.3 months (lymphadenectomy) *vs*. 58.7 months (no-lymphadenectomy)
Harter *et al*. [36]	Multicenter prospective randomized trial	647 patients with advanced ovarian cancer with macroscopic complete resection und clinically negative lymph nodes; Lymphadenectomy (n = 323) or no-Lymphadenectomy (n = 324)	Median overall survival 69-month (Lymphadenectomy) *vs*. 66 months (no-Lymphadenectomy); Progression-free 26 months in both group; Post-op complication Lymphadenectomy 12.4% *vs*. no-Lymphadenectomy 6.5%; Mortality at 2 months: 3.1% (Lymphadenectpmy) *vs*. 0.9% (No-Lymphadenectomy)

ovarian cancer, and has called into question the increased morbidity and mortality in systematic lymphadenectomy. The LIONs trial has also limited the surgical procedure after an initial chemotherapy to a total hysterectomy with bilateral adnexectomy and supracolic omentectomy, along with inspection and palpation of the entire peritoneal and retroperitoneal cavity. This surgical procedure should be followed by two to three cycles of platinum-based chemotherapy.

According to the European Society for Medical Oncology (ESMO) guidelines, standard surgical treatment for borderline ovarian cancer includes LND of pelvic and para-aortic regions up to the level of the renal vessels for staging purposes. However, there is no indication for restaging surgery if the nodal status does not alter management once a borderline ovarian cancer is confirmed by pathology results after adnexectomy [37].

Table 2 (Ref. [28–30,36]) is a summary of the main results for ovarian cancer.

2.4 Cervical Cancer and Lymph Node Dissection

Cervical cancer initially spreads to regional pelvic lymph nodes [38]. The first extra pelvic site of spread in the para-aortic area is involved in 12–25% of the cases [39].

Lymph node status is considered to be the most important prognostic factor in cervical cancer [40]. In particular, radical hysterectomy with pelvic lymph node dissection (PLND) is the standard treatment for stage IB and lower cervical cancer [41]. However, in early-stage cervical cancer, SLN dissection offers remarkable advantages, including a low false negative rate, identification of possible ectopic metastatic sentinel nodes, and the ability to detect micromestastasis [42]. Complications of PLND include intraoperative hemorrhage, ureteral injury, and nerve damage, as well as postoperative lymphocele or lymphoedema [4,43]. In addition, pelvic lymphadenectomy increases risk of oedema, pain or heaviness of the lower limbs, especially with the increase of the number of nodes removed [44,45]. According to Giuliano *et al.* [46], SLN biopsy has not shown to reduce morbidity in patients with cervical cancer, compared with complete lymph node dissection. However, the Senticol 2 trial, a multicenter randomized controlled trial demonstrated that SLN biopsy is associated with reduced early morbidity and improved quality of life [42].

Radio-chemotherapy has proved its efficacy in locally advanced cervical cancer (stages IIB and above). However, para-aortic LND remains important in advanced stages, whenever Positron emission tomography scan results reveal no macroscopic lymph node lesions. In the event of a positive paraaortic lymph node detection, radiation fields should be extended to the para-aortic level [47].

A meta-analysis by Thelissen *et al*. [38] revealed that in cases where imaging did not show suspicious pelvic aortic lymph nodes, pelvic aortic LND still identifies nodal metastasis in 12% of patients, with locally advanced cancer and in 21% of patients with pelvic nodal metastasis. This meta-analysis demonstrated that laparoscopic PLND upstages cervical cancer in cases where imaging suggested pelvic lymph node metastasis [38].

A study was conducted by Petitnicolas *et al*. [48] to investigate the feasibility lymphadenectomy of the inferior mesenteric artery aera in advanced cervical cancer. The rate

Table 3. Summary of main article for cervical cancer.

Article	Type	Patients	Conclusion
Petitnicolas *et al*. [48]	Retrospective study	119 patients para-aortic lymphadenectomy	Inferior mesenteric lymph node dissection group had shorter operative time 174 min *vs*. 209 mins
		Inferior mesenteric artery *vs*. infrarenal lymphadenectomy	No difference on intraoperative and postoperative complications, overall survival and progression free survival
Mathevet *et al*. [42]	Multicenter randomized trial	206 patients Sentinel lymph node arm (105) or Sentinel lymph node + Pelvic lymph node dissection (101)	Sentinel lymph node reduced early stage morbidity and improved quality of life
Tu *et al*. [49]	Prospective multicenter randomized	>600 patients. IA1, IA2, IB1, and IB2 cervical squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma	Results in 2026

of metastases above the inferior mesenteric artery is known to be low in advanced cervical cancer. This study included 119 women who underwent para-aortic lymphadenectomy and were affected to either inferior mesenteric artery level group or infrarenal lymphadenectomy level group. Patients in the inferior mesenteric artery group presents a statistically significant shorter operating time with a p-value = 0.001 (174 min *vs*. 209 min). However, no significant difference was found with regards to intra- and post-operative complications, overall survival, and progression free survival [36]. Thus, lymphadenectomy of the inferior mesenteric artery area is feasible in such cases due to its shorter operative time with no impact on survival rate and morbidity [48].

Currently, a prospective multi-center randomized trial is being conducted by Tu *et al*. [49] to compare SLN biopsy with lymphadenectomy in early-stage cervical cancer (PHENIX/CSEM 010). The hypothesis is that SLN biopsy does not reveal inferior oncological outcomes compared to lymphadenectomy, the primary endpoint being: disease-free survival. All patients will undergo radical hysterectomy and will be divided into either PHENIX I or PHENIX II group according to SLN status. Results are expected by 2026 [49]. This study seems promising and will certainly have an impact on the surgical management of early-stage cervical cancer.

Table 3 (Ref. [42,48,49]) represents a summary of the main results for ovarian cancer.

Fig. 1 is an overall summary of the main take home messages regarding this topic.

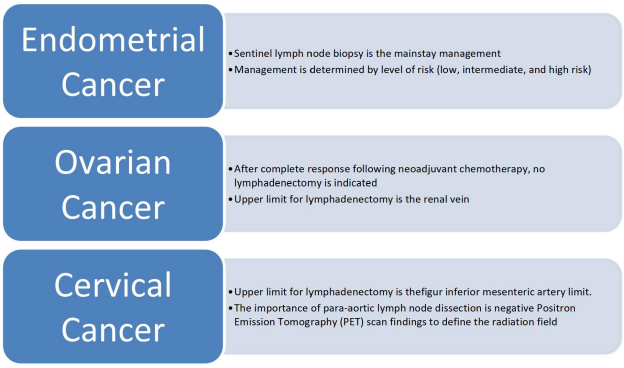

Fig. 1. A brief overview with the most important take home messages.

3. Conclusions

In conclusion, lymphadenectomy in gynecological malignancies remains a cornerstone in metastasis diagnosis, an important prognostic factor, and a reliable guide to management strategies. However, we cannot deny the fact that its associated morbidity renders systematic lymphadenectomy questionable with a remarkable shift towards SLN biopsy especially in endometrial cancers. In cervical cancers, limiting lymphadenectomy to the inferior mesenteric artery limits also seems promising, and studies are currently being conducted to study the feasibility of SLN dissection instead of systematic lymph node dissection. Similarly, in ovarian cancer patients, the LIONs study has revolutionized standard management plans by highlighting the increased morbidity and mortality in patients undergoing systematic lymphadenectomy.

Thus, is the associated morbidity due to systematic lymphadenectomy justifiable? Does it really improve survival rates and progression free survival compared to SLN biopsy and palpable lymph node dissection? Or is it time to switch into an era where less is better in terms of LND and gynecological malignancies?

Author Contributions

Conceptualization: NH, GM, JH. Interpretation of data: GM and JH. Validation: GC, FF, VC, RRN, RD, LM. Writing and original draft preparation: GM and JH. Writing - review and editing: FF. All authors contributed to editorial changes in the manuscript. All authors read and ap-

proved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Liliana Mereu is serving as one of the Editorial Board members/Guest editors of this journal. We declare that Liliana Mereu had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Felix Wong.

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