The role of lymph node dissection in endometrial cancer: a systematic scoping review.

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July 24, 2020

Abstract

Background: Surgical staging including lymph node dissection (LND) is considered the gold standard method of evaluating LN status and guiding adjuvant therapy in endometrial cancer (EC). The standard surgical treatment of EC includes systematic LND, which is associated with morbidity. Consequently, there is debate weighing the risks and benefits of LND. Objectives: To evaluate the role of LND in all stages of EC. Search Strategy: Systematic search of MEDLINE up to 9th January 2020 including references of relevant studies. Selection Criteria: Published literature in English describing LND in EC. Data Collection and Analysis: 176 articles were screened by title and abstract to select those describing roles of LND in EC. Main Results: We confirmed the diagnostic role of LND and the benefits of risk stratifying early-stage EC patients, despite variations in stratification systems. Low and high-risk groups have well-established guidelines. The role of LND remains controversial in intermediate and high-intermediate risk groups. Sentinel lymph node dissection seems promising to prevent under-/over-treatment. In all risk groups, the prognostic role of LND is well-understood however therapeutic use is debatable. In most stages of advanced EC, LND is beneficial, except for non-bulky nodal disease. Variation exists in what constitutes adequate LN counts, targets and surgical methods. Conclusions: International standardisation of the definition of LND and further adoption of sentinel lymph node algorithms is required. Future research should investigate the need to stratify for bulky and non-bulky nodal disease in advanced EC. New RCTs are needed to guide revaluation of the ESMO-ESGO-ESTRO 2016 guidelines.

Funding

There were no costs associated with conducting or writing this review.

Keywords

Carcinoma of the endometrium: diagnosis, Carcinoma of the endometrium: surgery, Gynaecological surgery: gynaecological cancer, Clinical guidelines, Systematic reviews

Tweetable abstract

Controversial role of LND in some sub-groups of EC stages. Sentinel LND seems promising.

Introduction

Uterine endometrial carcinoma (EC) is the most common malignancy of the female reproductive tract in developed countries[(1)], with approximately 380,000 new cases worldwide in 2018[(2)].

Most patients present with early-stage (stage I/II)[(3)]endometrioid EC[(4)]. In contrast, advanced cancer (stage III/IV)[(5)] accounts for more than 50% of uterine-related deaths[(6)]. In order to guide management, a preoperative assessment is mandatory. This includes a full clinical history, pelvic examination, ultrasonography and endometrial biopsy or curettage to determine histotype and grade. Additionally, advanced imaging is recommended to assess myometrial invasion[(5)].

Lymph node (LN) metastasis is the most common site of extrauterine spread in EC[7] and contributes to a worse survival outcome. LN involvement is the most important prognostic factor in EC, especially for early clinical stages[8]. Due to their high specificities[9], specialised imaging techniques such as pelvic CT, MRI and PET scan are recommended to determine LN status[5]. However, detection rates of node positive disease and availability to provide imaging to all early-stage EC patients remains variable between centres[10]. Hence, imaging alone is not sufficient for the surgical staging process[11].

The standard treatment of EC is total hysterectomy, bilateral salpingo-oophorectomy and in some cases systematic lymph node dissection (LND). LND is the surgical removal of lymph nodes[12]. Complete surgical staging, including LND is considered the gold standard method of evaluating lymph node status[7,13,14]. This can be used to assess patient prognosis and guide treatment decisions. LND has been demonstrated to have a possible diagnostic, prognostic and therapeutic benefit in patients with EC[12]. However, LND is associated with surgically related morbidity[12], leading to studies considering whether LND is required.

It is evident from the breadth of the literature that clinicians worldwide must balance the benefits and harms of LND. Therefore, we aim to conduct a scoping review evaluating the roles of LND in all stages of EC particularly addressing the key controversies.

Methods

Step 1: Identification.

Authors independently conducted literature searches of the MEDLINE database until 9 January 2020. From these, a comprehensive search strategy was derived consisting of the following MeSH terms and their relevant subheadings: "Endometrial Neoplasms", "Lymph Node Excision", "Lymph Nodes" and "Treatment Outcome". "Management" and "Outcomes" were included as non-MeSH terms. "English and Humans only" was applied as a filter. In Step 3, list of references of articles were also searched.

Step 2: Article selection.

Each author screened an equal number of citations by title and abstract. All primary studies and systematic reviews that reported LND as a primary intervention in a sample of women with EC confined to the uterus were included.

Step 3: Data-charting.

The full texts of all potentially relevant articles were reviewed collectively by the authors. A data-charting table was used to extract the following information from each article: general data (title, year of publication, author's name and journal name); methodological data (type of study, sample size, patient characteristics e.g. stage of EC); and clinical data (use of risk stratification tool, roles of LND identified, effectiveness of LND in these roles, clinical outcomes e.g. survival, any alternatives to LND mentioned).

Step 4: Summarising articles.

The data-charting table was constantly updated as the new roles of LND and "other" categories emerged. From articles that demonstrated a clear role of LND in EC, articles were organised into the following roles: 'diagnostic', 'prognostic', 'therapeutic', 'to guide treatment decisions' and 'to quantify treatment success'. "Other" categories included: 'alternatives to LND', 'methods of conducting LND', 'differences in LN targets' and 'treatments of advanced EC'. A critical appraisal of the included studies was conducted using the Critical Appraisal Skills Programme (CASP) checklists[15].

Figure 1 summarises the results of Steps 1-4 based on the PRISMA Extension for Scoping Review checklist[16].

Results and discussion

PRISMA flow diagram

Figure 1 | PRISMA flow diagram detailing search strategy and article selection process for the scoping review. This figure was created based on the PRISMA 2009 template flow diagram[17].

Summary of perspectives

Table 1 | Summary of perspectives of the critical review.

The diagnostic role of lymph node dissection in early-stage endometrial cancer

LND is used in the surgical staging of EC. The International Federation of Gynaecology and Obstetrics (FIGO) classification system is the most widely accepted method for EC staging. It was refined in 2009 based on advancements in the literature (Table 2)[18].

Table 2 | This table was adapted by the authors from Table 3 of The International Federation of Gynaecology and Obstetrics (FIGO) classification system[19]. EC = endometrial cancer. *Either G1, G2 or G3.

A key diagnostic role of LND in EC is to guide adjuvant treatment[20]. The ASTEC study (A Study of the Treatment of Endometrial Cancer) (2009) is one of two randomised controlled studies in this field. Given the low node-positivity rate in this study, a large number of patients would be required for adequate power. However, this requirement was not fulfilled as out of 683 patients in the standard surgery group and 686 in the LND group, only 9 and 54 patients respectively, were node-positive. The ASTEC study concluded that LND cannot be recommended in stage I EC unless it affects adjuvant therapy[20]. They therefore did not resolve an important clinical question: do higher risk patients benefit from LND?

A review by Todo et al[18] highlighted the importance of stratifying patients by risk and not staging alone because within each stage, different risk groups have different outcomes to treatments. The ESMO-ESGO-ESTRO 2016 consensus recognises this importance. It does so by incorporating other pathological prognostic features alongside FIGO 2009 to identify patients at risk of LN metastasis or recurrence[5]. During diagnostic investigations, clinical and aforementioned features are gathered and collated. This is used to stratify patients into risk groups. The defining features and management recommendations for early-stage EC based on ESMO-ESGO-ESTRO 2016 are summarised by risk group in Table 3.

The features that define "low-risk" are varied within the literature, resulting in differences in how surgical management and adjuvant therapies were tailored, as seen in this systematic review[21]. For the low-risk group, FIGO 2009[19] and National Comprehensive Cancer Network (NCCN) 2016 identify tumour diameter as an important pathological feature in addition to those in ESMO-ESGO-ESTRO 2016 (Table 3). A 2017 study also incorporated tumour size of less than 2cm into its risk stratification system, however this was not found to be an independent prognostic factor[12,22]. Without a standardised approach, this poses difficulty both in the clinical setting and when comparing clinical trials.

Table 3 | Summary of ESMO-ESGO-ESTRO Consensus Conference 2016 risk stratification system for early-stage endometrial cancer. The figure was created by authors based on ESMO-ESGO-ESTRO Consensus Conference 2016[5]. Depth of myometrial invasion: Stage IA = Superficial <50%; Stage IB = Deep [?]50%. Cervical involvement: Stage II. EBRT = external beam radiation therapy.

The prognostic role of lymph node dissection in early-stage endometrial cancer

The prognostic role of LND is universally accepted in early-stage EC. LN metastasis is the most common site of extrauterine spread[7] and an important prognostic factor associated with EC[13]. LND increases the prognostic value of the FIGO 2009 staging system[23] and is more accurate than preoperative imaging or palpation of LNs[13,14]. It provides precise prognostic information, guiding the need for adjuvant radiotherapy, chemotherapy or both[13,24] In women with negative LNs, unnecessary adjuvant treatment can be prevented[7].

Low-risk group

Based on current ESMO-ESGO-ESTRO 2016 risk groups, patients with low-risk EC should not undergo LND as part of the staging process[25] (Table 3). In the low-risk group, considering there is a very low (0.8%)

associated risk of LN metastasis[26,27], there is a need to consider the short and long-term morbidities of LND[14,24]. However, a minority of studies suggest detection of occult LN metastasis is essential for prognosis, as 4.1–5.6% of low-risk EC patients may have LN metastasis[13,28]. LNs are one of the most common sites of relapse, with 90% patient mortality[29]. LND can provide better prognostic information on patients with low-risk EC at risk of disease recurrence, improving outcomes[29].

Intermediate and high-intermediate risk groups

LND is vital to bridge the gap between pathological prognostic features such as lymphovascular space invasion (LVSI) and adjuvant therapy. ESMO-ESGO-ESTRO 2016 outlines adjuvant therapy recommendations in considerable detail for the latter two sub-groups of intermediate risk patients. LND could therefore be considered justified in this case. However, in the first sub-group (LVSI-positive, G1/2 and superficial myometrial invasion (<50%)), even if LND is commenced, guidelines for adjuvant therapy are not clear (Table 3).

A matched-pair retrospective study highlighted that a low proportion of intermediate-risk patients who underwent LND had positive LNs compared to unstaged patients[30]. Furthermore, across all risk groups, surgery-related adverse effects of LND must not be ignored[29]. Specifically in the intermediate risk group, postoperative complications such as lymphocyst formation and lower-limb lymphoedema were significantly higher in the LND group[30–32]. Interestingly however, infection rates were higher in unstaged patients, perhaps because non-surgical infections were also included[30].

Ultimately, there is conflicting evidence comparing the benefit of knowing the LN status to the adverse effects of LND.

High risk group

LND is recommended in high-risk EC according to ESMO-ESGO-ESTRO 2016[25] (Table 3). In the high-risk group, the prevalence of LN involvement is ~19.3%[13]. In these patients, worse prognosis can be assumed without LND, with a need for adjuvant treatment guided by node-positive disease[13]. Furthermore, without surgical staging including LND, treatment relies on increased use of external beam radiation therapy (EBRT) which is associated with a much higher morbidity than with LND alone[33]. While chemotherapy may improve the prognosis of node-positive patients, this is not applicable to node-negative patients, further demonstrating the importance of pathological LN assessment in making adjuvant treatment decisions[33].

The therapeutic role of lymph node dissection in early-stage endometrial cancer

Low risk group

The ESMO-ESGO-ESTRO 2016 recommendations state no therapeutic benefit of LND for low-risk EC patients (Table 3). These recommendations are based on a study by Benedetti et al.[34], which concluded that systematic pelvic LND did not improve 5 year disease free survival (DFS) or overall survival (OS). However, these recommendations are limited as this RCT did not risk stratify their patient cohort. The second RCT was the ASTEC trial[20]. The "low-risk" group was defined as FIGO 1988 IA or IB and G1 and G2, which differs from the current ESMO-ESGO-ESTRO 2016 classification (Table 3). Results showed no survival benefit (OS and recurrence-free survival (RFS)) of pelvic LND in "low-risk" patients. In this trial, para-aortic node sampling was at the discretion of the surgeon, and in patients with anaesthetic concern or obesity, the surgeon may have omitted dissection of some LNs. A reduced number of lymph nodes dissected is a significant predictor of progression free survival (PFS) and OS[5,21]. These significant limitations may have contributed to the lack of therapeutic benefit shown, mistakenly supporting ESMO-ESGO-ESTRO 2016 recommendations. Additionally, a meta-analysis of seven observational studies[21]showed limited survival benefit with LND in low risk patients.

Intermediate-high risk group

The pathological inclusion criteria used by Benedetti et al.[34] were FIGO 1988 Stage IB and G1, satisfying current intermediate and high-intermediate risk groups. They reported that pelvic LND did not improve

5-year DFS or OS. Para-aortic LND and the use of adjuvant therapies was left to the discretion of the clinician, both of which may have influenced metastasis and therefore survival. A recent matched-pair study that focussed specifically on intermediate risk patients supported the findings of Benedetti et al. with the addition that post-operative morbidity was similar in both groups[30]. Although a risk stratification system similar to ESMO-ESGO-ESTRO 2016 was adopted, cervical involvement was considered as an additional defining feature[35].

Before ESMO-ESGO-ESTRO 2016, multiple studies like the previously discussed ASTEC 2009, combined both intermediate and high-risk groups[20,36]. We have followed suit for the purposes of standardisation. The ASTEC trial showed no benefit of pelvic LND in terms of RFS and OS. Alternatively, surgical staging including LND demonstrated improved survival in a large patient cohort with intermediate-high risk EC[36]. This study was limited by its retrospective nature and therefore could not account for confounding factors such as comorbidities. Similar findings were observed in a retrospective multicentre study with the new ESMO-ESGO-ESTRO 2016 high-intermediate risk group[37].

The role of lymph node dissection in advanced endometrial cancer

Advanced EC is defined as stage III or IV endometrial carcinoma of any histology[5]. LND has proved efficacious in diagnosing advanced cancer in high-risk patients[5], tailoring adjuvant therapy for those with adverse pathological features[33] (Table 3). LND also has a vital prognostic role in advanced EC[25,38]. These findings are supported by a multicentre study, which concluded that LN ratio (the proportion of metastatic LNs to the total number of removed LNs) is the strongest independent prognostic parameter in stage IIIC patients. LN ratio of $<$10% and $>$50% are associated with a significant difference in 5-year OS[25].

In stage IIIC EC, a recent study by Multinu et al. concluded that LND can be omitted from surgical staging of "non-bulky" nodal disease as combined adjuvant therapy (chemotherapy and EBRT) proved to be effective alone[39]. This result cannot be extrapolated to "bulky" and "suspicious nodes", as these were not included in this study. This novel finding differentiates "bulky" and "non-bulky" nodal disease previously unmentioned by ESMO-ESGO-ESTRO 2016, although Multinu et al. fails to define these terms clearly. Other studies have defined bulky nodal disease as $>$1cm[34]. Nonetheless, this may reinforce the therapeutic benefit of LND specifically in advanced bulky nodal disease. For stage III EC, the ESMO-ESGO-ESTRO 2016[5] supported by the newer SEOM guidelines[40] recommend radical cytoreductive surgery (debulking), which is defined as reducing the volume of a tumour to the greatest extent possible[41]. The Gynaecologic Oncology Group (GOG) recommends reducing gross residual disease to [?]1cm[41]. In addition, LND prior to cytoreductive surgery resulted in better survival outcomes[42,43].

The effect of LND on non-endometrioid type cancers is not well-characterised given the low number of this histological subtype[39]. Therapy options are limited for advanced EC with extra-abdominal metastases, and there is no widely acknowledged agreement regarding treatment of stage IVB EC[5,44]. Therefore, the prognosis for stage IVB EC remains extremely poor with the 5-year disease specific survival (DSS) of ˜5%. In this case, aggressive cytoreductive surgery to reduce tumour size could be beneficial[45].

What defines adequate lymph node dissection?

The definition of LND as part of surgical staging varies greatly between studies with a lack of international standardisation[46].

Lymph node counts

LN removal counts provide a way of measuring the adequacy of surgical staging to guide adjuvant therapy and prognosis[5,33]. Improved OS is related to a higher number of LNs removed, especially in patients with high and intermediate risk EC[36]. Literature shows a wide range of LN removal counts[20,34] suggesting the subjective definition of adequate LND is biased when evaluating its prognostic and therapeutic efficacy. Studies have shown that patients have improved survival when $>$10–12 LNs were removed[5,33]. In contrast one study suggested that 21–25 nodes are required for adequate nodal assessment[38]. This was directly opposed by Benedetti et al. showing no improved survival with removal of 20 or more LNs[34]. These

mixed findings support the ESMO-ESGO-ESTRO 2016 consensus that systematic LND should be defined by removing more than 10 LNs[5]. This calls into question the ASTEC trial in which less than 10 LNs were removed in 35% of surgeries[20].

Lymph node targets

LND in EC patients can include different LN targets. Mariani et al. reported the potential therapeutic role of pelvic and paraaortic LND in node positive low risk patients with EC[47]. Of the node positive patients, 84% had pelvic LN metastases and 67% had para-aortic node metastases. They concluded that there is a need for systematic pelvic and para-aortic LND. This finding is supported by a study which investigated the anatomical pattern of LN metastases in patients with high-risk early or advanced EC[48]. Patients underwent systematic pelvic and para-aortic LND and LNs were histologically assessed. It was found that 18% of patients had positive pelvic nodes, 14.8% had positive para-aortic nodes, and 3.1% had isolated positive para-aortic nodes. Despite the low prevalence, special attention is warranted for the latter group to avoid possible misdiagnosis in stage I-II EC[24]. This distribution of positive nodes indicates that LND, if performed, should contain both pelvic and para-aortic nodes up to the renal vessels for an accurate assessment of all potentially positive nodes[5,48]. Previous studies assessing the efficacy of LND as a treatment did not include para-aortic nodes[20].

Surgical method

EC surgical staging including pelvic and paraaortic LND can be conducted by minimally invasive surgery (MIS) or open laparotomy[49]. MIS has been associated with less complications with a reported overall rate of 7%[49]. However, extent of LND was unreported in all arms of this study, a potentially significant confounder[49]. The other benefits of MIS are well documented such as shorter hospital stay and faster recuperation than laparotomy[46,50], as recommended by ESMO-ESGO-ESTRO 2016 (Table 3) and further supported by a recent RCT[46]. Open laparotomy now tends to be used in EC patients with increased complexity including obese patients, G3 and G4 tumours and higher uterine weight[51].

MIS is inclusive of robotic and laparoscopic surgery. Despite the safety and feasibility of robotic surgery becoming widely accepted, it represents a recent technology with reduced user experience[52]. Looking at various parameters of patient outcome, there are limitations such as increased cost and operative time[51,52], a factor very much dependent on the surgeon's experience.

Robotic surgery is found to have a significantly reduced learning curve compared to laparoscopy and improved intraoperative and major complications[50]. This is however opposed by multiple studies displaying no difference in complications between the different surgical techniques[52,53]. A retrospective cohort study did demonstrate however, reduced urinary tract injuries in the robotic patient group despite the same overall rate of intra- and postoperative complications[52]. Despite these findings, the study did not place enough attention on long-term health parameters such as return to work, quality of life and OS[52]. Comparing robotic and laparoscopic conversion to open laparotomy, there are mixed findings. Some studies find a lower rate of conversion for robotic[50,52,54] but other retrospective studies found laparoscopy to have lower rates[51] or no difference between the surgical methods[53].

Thirty-day readmissions rates between methods were similar[51,52]. However, readmission rates outside of the primary hospital were unknown[51]. Robotic surgery is widely associated with shorter hospital stay and blood loss[50,52,55]. Reduced pain may factor into the lower hospital stay allowing patients to be mobilised faster[55]. In multiple studies, the reduced blood loss was not clinically significant because blood transfusion rates were unaffected[50,52,55]. Yet one of these studies suggested that the reduced blood loss could reflect decreased complications and increased ability to deal with difficult anatomy[55].

In summary due to the variations in morbidity[49], further review of minimally invasive LND surgical methods is needed.

Role of sentinel lymph node dissection

In early-stage EC, systematic LND plays a role in complementing preoperative imaging and is fundamental to guide adjuvant treatment. Sentinel lymph nodes (SLN) are the first to be involved with metastatic cancer cells and therefore require detailed examination known as ultrastaging[56]. This procedure involves SLN dissection (SLND) and biopsy guided by SLN mapping[3]. A variety of SLN algorithms have shown similar diagnostic accuracies to MRI[57] and systematic LND[58], therefore ESMO-ESGO-ESTRO 2016 recognises SLND as a relatively novel alternative to systematic LND.

Since 2016, the significance of SLND due to its enhanced benefits have been further substantiated. In high-risk patients, SLN mapping has shown high detection rates of LN metastases[59]. However, this study demonstrated a false-negative rate of 22%, perhaps due to its small (n = 53), single-centre study design. The Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) trial is the largest multicentre prospective study to date investigating the accuracy of SLND in multi-risk stage I patients. They concluded that their SLN algorithm presented high diagnostic accuracy with a much reduced false-negative rate of 3%[60]. A further study directly compared SLND to LND[49]. It reported reduced rates of readmission as well as decreased incidence of postoperative complications in the SLND group. In contrast, high grade and non-endometroid EC patients (confirmed on final histology) displayed failure in the mapping process[61]. Overall, SLND has shown promising results in early-stage EC however, better recognition and adoption may aid optimisation of SLN algorithms[3,60].

Limitations

This scoping review used secondary data in line with our article selection criteria. Our conclusions only represent the reported findings of the original authors. Specific limitations of individual studies have been discussed above.

Conclusion

In this scoping review, we have critiqued the role of LND, with variations observed by stage, on both prognostic and therapeutic levels.

There is a lack of international standardisation for both early-stage risk stratification systems and definition of LND. Whilst definitive guidelines like ESMO-ESGO-ESTRO 2016 exist for low and high-risk groups, the role of LND and use of subsequent adjuvant therapy is controversial for intermediate and high-intermediate risk groups. The mixed nature of findings suggests the need for a series of prospective randomised trials. These would need to consider multiple pathological features, in each sub-group of intermediate risk. In addition, studies validating adjuvant therapy modalities may confirm the role of LND. SLND provides a potential solution finding a balance between undertreating and the adverse risks associated with LND.

Previously it has been widely accepted that LND is diagnostically, prognostically and therapeutically beneficial in advanced stage EC with the exception of stage IVB EC where cytoreductive therapy is recommended instead. However, new evidence has found no benefit for LND in non-bulky advanced EC. Future research on the need to stratify according to bulky and non-bulky nodal disease may help to reach a consensus on tailoring treatment for advanced EC patients.

Acknowledgments

The authors would like to thank the anonymous peer-reviewers and academics alongside the invaluable support and guidance provided by the Reproductive and Developmental Sciences BSc pathway leads at Imperial College London.

Disclosure of interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Contribution to authorship

AK, FTW, MA and TU contributed equally to conceive, design and oversee the conduct of this review. This included executing the literature search, acquisition, analysis and interpretation of the literature. AK critically reviewed 'the diagnostic role', FTW 'the prognostic role', MA 'the therapeutic role' and TU 'intermediate-high risk group' for the latter two 'role' categories. All authors were involved in drafting the first revision of the manuscript, critically responding to peer-reviewer's comments (Supplementary information 1) and producing the amended revision that is this manuscript. We certify that all authors are responsible for the content of this manuscript and have read and approved of the final version. Order of authorship was decided alphabetically.

Details of ethics approval

Ethical approval was not required.

Word count

Abstract: 250 words

Tweetable abstract: 91 characters

Main body of text: 3450 words

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Perspective title	Perspectives summary
The diagnostic role of lymph node dissection in early-stage endometrial cancer	**LND should be used to guide adjuvant treatment[15]** by stratifying patients by risk and not staging alone[16]. **LND shows varied use in guiding adjuvant treatment** because pathological prognostic features differ between different risk stratification systems[12,17].
The prognostic role of lymph node dissection in early-stage endometrial cancer	**Low risk group:** LND is not warranted in EC staging based on the ESMO-ESGO-ESTRO 2016 as there is a very low risk of LN metastasis[18,19]. LND may be warranted in EC staging to detect occult LN metastasis[20]. **Intermediate and high-intermediate risk groups:** LND is not warranted in EC staging as patients present with a low proportion of positive LNs[21] with unclear guidelines for adjuvant therapy[5]. LND may be warranted in EC staging when adjuvant therapy is recommended[5]. **High risk group:** LND is warranted in EC staging based on the ESMO-ESGO-ESTRO 2016 due to high prevalence of lymph node involvement[22]. Without LND, treatment would rely solely on radiation and chemotherapy[23].
The therapeutic role of lymph node dissection in early-stage endometrial cancer	**Low risk group:** There is no therapeutic benefit to LND based on the ESMO-ESGO-ESTRO 2016[20], although the evidence supporting these guidelines misclassify low risk patients[15,24]. **Intermediate – high risk groups:** While LND demonstrated improved survival in a large patient cohort[25,26], there is no therapeutic benefit to LND[15,24].
Role of lymph node dissection in advanced endometrial cancer	**LND is beneficial in advanced EC based on ESMO-ESGO-ESTRO 2016.** LND is effective at diagnosing advanced EC and tailoring adjuvant therapy[27]. Patients benefited from undergoing LND, before debulking therapy[28]. LND is used to calculate LN ratio, the strongest independent prognostic parameter in stage IIIC EC[29]. **LND is not beneficial in advanced EC.** LND may be omitted for non-bulky advanced EC patients receiving appropriate adjuvant therapy[30]. There is no consensus regarding the treatment of stage IVB EC[31].

Perspective title	Perspectives summary
What defines adequate lymph node dissection?	**Lymph Node Counts:** Improved survival is correlated with >10 LNs being removed by LND based on ESMO-ESGO-ESTRO 2016[5,24,27]. Alternatively, improved survival is thought to correlate with >20 LNs being removed by LND[32]. **Lymph Node Targets:** There is a need for pelvic and para-aortic LND[33] up to the renal vessels[34] based on ESMO-ESGO-ESTRO 2016. Special attention is needed for isolated positive para-aortic LNs[35]. **Surgical Method:** Minimally invasive surgery (MIS) is preferred over laparotomy based on ESMO-ESGO-ESTRO 2016[5,36–38] while laparotomy is preferred for complex cases[39]. Within MIS, robotic and laparoscopic LND shows similar adequacy[38–40] while robotic has certain advantages over laparoscopic surgery[38,41,42]. **Role of sentinel lymph node (SLN) dissection:** ESMO-ESGO-ESTRO recognises SLN algorithms as a potential alternative to systematic LND in early stage EC[5,43] supported by recent studies[23,36,44].

Table 1 | Summary of perspectives of the critical review.

Early EC	**Stage I*: Tumour confirmed to the uterus**	**Stage I*: Tumour confirmed to the uterus**	**Stage I*: Tumour confirmed to the uterus**
	IA*	IA*	No or <50% myometrial invasion (superficial)
	IB*	IB*	[?]50% myometrial invasion (deep)
	Stage II*: Tumour invades cervical stroma, but does not extend beyond the uterus	**Stage II*: Tumour invades cervical stroma, but does not extend beyond the uterus**	**Stage II*: Tumour invades cervical stroma, but does not extend beyond the uterus**
Advanced EC	**Stage III*: Local and/or regional spread of the tumour**	**Stage III*: Local and/or regional spread of the tumour**	**Stage III*: Local and/or regional spread of the tumour**
	IIIA*	IIIA*	Tumour invades the serosa of the uterus and/or adnexae
	IIIB*	IIIB*	Vaginal and/or parametrial involvement
	IIIC*	IIIC*	Metastases to pelvic and/or para-aortic lymph nodes

Early EC	**Stage I*: Tumour confirmed to the uterus**	**Stage I*: Tumour confirmed to the uterus**	**Stage I*: Tumour confirmed to the uterus**
		IIIC1*	Positive pelvic nodes
		IIIC2*	Positive para-aortic lymph nodes with/without positive pelvic lymph nodes
	Stage IV*: Tumour invades bladder and/or bowel mucosa, and/or distant metastases	**Stage IV*: Tumour invades bladder and/or bowel mucosa, and/or distant metastases**	**Stage IV*: Tumour invades bladder and/or bowel mucosa, and/or distant metastases**
	IVA*	IVA*	Tumour invasion of bladder and/or bowel mucosa
	IVB*	IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Table 2 | This table was adapted by the authors from Table 3 of The International Federation of Gynaecology and Obstetrics (FIGO) classification system[17].

EC = endometrial cancer. *Either G1, G2 or G3.

	Defining risk groups: pathological prognostic features	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Management recommendations**	**Management recommendations**	**Management recommendations**
Risk groups	**Tumour differentiation grade**	**Histological type**	**FIGO 2009 stage**	**LVSI**	**LND**	**Adjuvant therapy**	**Surgical method**
Low risk	G1 / G2	Endometrioid	IA	Negative	No	No	Minimally invasive approach preferable

	Defining risk groups: pathological prognostic features	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Management recommendations**	**Management recommendations**	**Management recommendations**
Intermediate risk	G1 / G2		IA	Positive	Prognostic benefit: can be considered for staging purposes *[Therapeutic benefit: uncertain]*	No recommendations	
	G1 / G2		IB	Negative		Adjuvant brachytherapy / no adjuvant treatment for <60 years old	
	G3		IA	Negative		If node negative confirmed by surgical staging: same as above If no surgical nodal staging: adjuvant brachytherapy alone	
High-intermediate risk	G3		IA	Positive		No surgical nodal staging: adjuvant EBRT	
	G1 / G2		IB	Positive		No recommendations	

	Defining risk groups: pathological prognostic features	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Defining risk groups: pathological prognostic features**	**Management recommendations**	**Management recommendations**	**Management recommendations**
High risk	G3		IB	Negative / positive	Prognostic benefit: Yes *[Therapeutic benefit: uncertain]*	If node negative confirmed by surgical staging: adjuvant EBRT with limited fields / adjuvant brachytherapy If no surgical nodal staging: EBRT and chemotherapy in combination is preferred over giving either treatment alone	
	G3	Non-endometrioid	IA / IB	Negative / positive		See advanced endometrial cancer section	
	G1 / G2 / G3	*Uncertain*	II	Negative / positive			

Table 3 | Summary of ESMO-ESGO-ESTRO Consensus Conference 2016 risk stratification system for early-stage endometrial cancer. The figure was created by authors based on ESMO-ESGO-ESTRO Consensus Conference 2016[(5)].

Depth of myometrial invasion: Stage IA = Superficial <50%; Stage IB = Deep [?]50%. Cervical involvement: Stage II.

EBRT = external beam radiation therapy.

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