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Evolution of retroperitoneal staging in endometrial cancer: narrative review and overview of literature

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ABSTRACT

Endometrial cancer (EC) is the most common female genital tract malignant cancer. Lymphatic staging is a major prognostic factor and the main predictor of recurrence. The aim of this review is to explore lymph nodal management in EC up to this day and understand how the new molecular EC classification may affect lymph nodal management. A search was conducted in December 2022 to find all relevant trials and shows how, over the years, staging techniques have evolved, becoming more accurate and less invasive. In 1996, a less invasive staging method was found: the Sentinel Lymph Node (SLN), safer and more reliable in detecting metastatic disease. To date, the available pieces of evidence suggests that lymphadenectomy should not be performed in all patients with EC because it does not increase Overall Survival (OS) or Disease Free Survival (DFS) compared to standard surgery without lymphadenectomy, while it actually increases the risk of postoperative complications, in all EC risk classes. In addition, SLN and lymphadenectomy do not have any difference in terms of Recurrence Free Survival (RFS) in patients with low volume disease. Moreover, data available in literature highlight that the molecular classification may play a more accurate prognostic role than histological analysis. Even though some studies showed that the molecular mutations were not significant predictors of recurrence, several large ongoing trials may set new treatment standards. In conclusion, we can state that SLN mapping is an optimal method of EC staging with good sensibility, specificity and decreased surgical complications. Instead, more studies are needed to understand how molecular mutations can affect lymph nodal management.

INTRODUCTION

Endometrial cancer (EC) is the most important female genital tract malignant tumor with 417,000 new diagnoses worldwide in 2020 and almost 100,000 deaths [1-3]. EC is more common in developed countries, where probably this could be attributed to obesity increase and diabetes; environmental, hormonal and genetic factors can also contribute to its development [4-6]. In the early stages, the expansion of EC is limited to the surrounding organs, such as the cervix and the myometrium, then it can spread through blood or lymphatic vessels to distant organs. In fact, lymph nodes positivity represents one of the most important prognostic factors [7], as well as myometrial invasion and grading, and the main predictor of recurrence [8]. The lymph node station primarily affected is the pelvic one (formed by the common, external and obturator lymph nodes) followed by the para-aortic lymph nodes [9-11]. There has been controversy regarding the role of lymphadenectomy for patients staging [12], especially with the introduction of the new EC classification. The main doubt is whether lymphadenectomy is needed for all patients, regardless of the severity of their condition, because especially in low-risk patients the rate of lymph node involvement is not high [13, 14]. For this reason, the use of Sentinel Lymph Node (SLN) has been established: SLN is the first lymph node to which cancer cells are most likely to spread from a primary tumour. SLN mapping has long been used in various cancers, such as breast cancer and melanoma; in 1996 it was introduced for EC, and it soon gained popularity [15]. Although international societies are starting to recognize the utility of lymph node mapping in EC, this staging practice is not recommended yet in the guidelines. The goal is to reduce the number of lymphadenectomies by removing only the affected lymph node rather than performing a more extensive lymph node dissection to staging [16], reducing all complications associated with lymphadenectomy [17].
The aim of this review is to explore lymph nodal management in EC to this day, according to the most relevant and latest studies, and to discover how the new molecular classification of EC may affect the future of lymph nodal management.

MATERIALS AND METHODS

The search was conducted in December 2022, by different authors independently, on different databases (MEDLINE, EMBASE, Global Health, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database and Web of Science) to find all relevant trials. No filter on the year of publication was set. We screened all articles including the following keywords: "endometrial", "endometrium", "cancer", "carcinoma", "sentinel lymph node", "lymphadenectomy", "lymph node mapping". Duplicates were removed as well as irrelevant articles. Titles and/or abstracts of studies retrieved using the search strategy, and those from additional sources, were screened independently by 2 review authors (A.C., E.D.A.) to identify studies that potentially meet the aims of this review.
Key criteria for inclusion were: 1) articles in English, 2) original studies about sentinel node mapping or lymphadenectomy for EC treatment, and 3) studies comparing sentinel node mapping or lymphadenectomy for EC treatment. The full text of these potentially eligible articles was retrieved and independently assessed for eligibility by other 2 review team members (T.G.D.A., G.D.B.). Any disagreement between them over the eligibility of particular articles was resolved through discussion with a third (external) collaborator.
All the studies screened through the inclusion and exclusion criteria were examined, and relevant data extracted for each paper. Two authors (I.C., L.S.) independently extracted data from articles about study characteristics and included populations, type of intervention and outcomes, using a pre-piloted standard form in order to ensure consistency. Due to the nature of the findings, we opted for a narrative synthesis of the results from selected articles.

RESULTS

Currently the choice of performing a surgical nodal staging and the extended lymphadenectomy is the matter of debate in the management of EC [18]. Various international guidelines recommend the execution of nodes status study, but no level A evidence supports the therapeutic role of pelvic and/or aortic lymphadenectomy for EC patients.
In 2008, Benedetti Panici *et al*. with a randomized clinical trial of 514 early-stage EC patients analysed whether the addition of pelvic systematic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improved Over-

all Survival (OS) and Disease Free Survival (DFS). Results of this trial demonstrated no difference in 5-year OS and 5-year DFS between two different approaches. According to these results, the recurrence rate between the two groups was similar as well as sites of first recurrence [13].
Similarly, the ASTEC trial confirmed these results [19]. Overall results were confirmed in 2010 [9], concluding that pelvic lymphadenectomy cannot be recommended as a routine procedure in early-stage EC [10, 19]. However, these trials had significant limitations: no homogeneity for the EC class of risk, few lymph nodes removed during the surgical procedure and adjuvant therapy administration that determined important biases of the results.
After defining the non-beneficial role of pelvic lymphadenectomy, various studies investigated whether more extensive nodal dissection could affect the survival of EC patients.
Although extensive lymph node dissection does not improve the oncological outcomes of patients with early-stage EC, the results about intermediate- and high-risk EC have been controversial. Some studies demonstrated that the para-aortic plus pelvic lymphadenectomy may decrease the risk of death and the recurrence rate and increase the 5-years OS and DFS [20-25].
For this reason, in the past years the advantages and disadvantages have been analysed. Among the complications of lymphadenectomy, the most frequent ones are lymphedema and lymphocele, lymphocysts, tingling, numbness and fatigue [26]. The incidence of lymphedema in the lower limbs is estimated at 30-40% and of the lymphocele is about 17.3%, most frequently located in the pelvic region and related to the number of lymph nodes removed [23, 24]. In addition, most patients with EC have personal risk factors, such as obesity, diabetes or metabolic syndrome that contribute to increased surgery-related complications. Tailored surgery and no overtreatment could reduce the incidence of these adverse events [29-35].
To address these limitations, Mariani *et al*. suggested to stratify patients according to various risk factors. From results of this retrospective study, lymphadenectomy does not play a beneficial role in patients with grade 1 and 2 endometrioid lesions with MI ≤ 50% and primary tumour diameter ≤ 2 cm [14].
Over the years, SLN mapping has become an acceptable surgical strategy to staging patients with EC, safer and less invasive than lymphadenectomy. The technique, approved for various types of cancer, as breast cancer and melanoma, allows to identify, by injection of a tracer, the first lymph node to which cancer cells are most likely to spread from a primary tumour through the lymphatic system [15]. Therefore, if the SLN, or first node, is negative for metastasis, then the ensuing nodes should also be negative [17]. For the detection of SLN, several techniques and tracers have been proposed. The tracer most commonly used is Indocyanine Green through cervical injection (CI) or hysteroscopic injection (HI). The first is performed by intracervical injections at 3 and 9 o'clock positions, both submucosally and deep into the CI stroma. In HI, the injection is performed at a subendometrial level, around the lesion, or at 3, 6, 9 and 12 o'clock [36]. After tracer injection, the SLN is identified by fluorescent imaging and then removed. In 2020, Ditto *et al*., comparing two techniques in a multicentric randomized trial of 151 patients with EC, supported the adoption of CI instead of HI injection, because the first allows better identification of SLN, especially in the pelvic area [37]. The FIRES trial demonstrated that SLN has high predictive value detecting metastatic disease in EC. With a sensitivity of 97.2% and a negative predictive value of 99.6%, LNS is equivalent to lymphadenectomy in the staging of endometrial cancer; it also has the potential to cause fewer side effects than lymphadenectomy [38].
The accuracy of SLN, validated for low-risk EC, was considered also in intermediate-risk and high-risk EC, as for other gynaecological malignancies [39]. In 2019, the SHREC trial, considering a cohort of 257 patients high-risk EC, demonstrated that the SNL method had an optimal sensitivity and negative predictive value (NPV) of 100% for both [40]. Almost overlapping results were confirmed in the SENTOR trial in the following years, analysing both the high and the intermediate risk EC [41]. Thus, even in this group of patients with higher risk of recurrence, SLN mapping performed by experienced surgeons should exclude overall lymph node involvement in almost 100% and safely replace lymphadenectomy in all EC risk classes.
According to recent retrospective studies, long-term oncological outcomes were assessed and no significant differences in terms of three-years DFS and OS were found among patients that received SLN, SLN plus lymphadenectomy or lymphadenectomy alone. Surgical-related complication, as cellulitis or lower extremity lymphedema, were less frequent with SNL surgical staging compared with lymphadenectomy [42-44].

The good accuracy of SLN mapping in the identification of EC with lymph node disease is certainly attributable to the concept of ultrastaging that identifies low-volume metastases, not detectable with conventional histological examination, as micrometastases and isolated tumour cells (ITC). Ultrastaging is performed by analysing two sections at 5-μm and 50-μm from disease-free tissue using both haematoxylin-eosin and monoclonal anti-human cytokeratin clone AE1/AE3.

Micrometastases and ITC refers to cluster and single cells of > 0.2 mm to ≤ 2 mm or ≤ 0.2 mm, respectively, according to the American Joint Committee on Cancer (AJCC) [45, 46]. Data from recent years report an increased number of patients with low-volume EC with pelvic and extrapelvic lymph node disease. To confirm these results or highlight some differences, several studies considered a large cohort of patients analysing all risk molecular classes. Overall results showed that SLN mapping improves detection of extra-uterine disease in low, intermediate and high-risk EC [42, 47].

However, numerous studies have evaluated the prognostic role of low-volume disease and to date some controversies have been highlighted. Bakes *et al*. in 2021 enrolled 175 patients with EC in stage IA/B and II with ITC comparing data between patients undergoing only SLN mapping and SLN mapping plus lymphadenectomy and possible adjuvant therapy: no adjuvant therapy or vaginal brachytherapy only, external beam radiation (EBRT) and chemotherapy with/without pelvic radiation. Results showed that extra-vaginal relapses rate were similar in patients with or without chemotherapy ($p = 0.68$), even receiving chemotherapy was not associated with decreased RFS compared to no adjuvant therapy/vaginal brachytherapy. The study also showed that the type of nodal staging did not affect RFS [48]. Ghoniem *et al*. in multi-institutional study enrolling a cohort of 247 patients with EC, with micrometastasis (n = 115) and ITC (n = 132) considering grade 3 disease, non-endometrioid histology and possible lymphovascular space invasion (LVSI) and/or uterine serosal involvement. Patients were divided according to no or different strategies of adjuvant therapy: vaginal brachytherapy only EBRT and/or chemotherapy with or without vaginal brachytherapy. Non-Endometrioid histology, LVSI and uterine serosal invasion were independent predictors of recurrence increasing the risk of recurrence by 4.81% in patients. Meanwhile, significant differences among the patients that did not receive adjuvant therapy and those who received adjuvant therapy were not demonstrated [49]. Another international multi-institutional comparative study published by Cucinella *et al*. included 200 patients with uterine-confined EC and intermediate risk factors demonstrated no significant difference in non-vaginal RFS between ITC *vs* node-negative patients. However, in a subanalysis they observed worse non-vaginal RFS in patients with concurrent ITC and LVSI. In particular, the 4-year RFS was 64.6% in this subgroup compared to 93.3% and 91.7% for the node-negative patients with and without LVSI, respectively [50]. Probably the LVSI has a higher impact on RFS than the adjuvant therapy in those patients with EC and ITC. However, longer follow-up time and a larger sample size are needed before definitive recommendations regarding adjuvant therapy for patients with EC and only ITCs in SLN can be made.

To date the current molecular classification allows for tailored therapy for EC patients. In 2020 European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy & Oncology (ESTRO), European Society of Pathology (ESP) guidelines proposed a new classification of EC based on histopathological features and four different mutational status type identified by The Cancer Genome Atlas (TCGA): abnormal p53 (p53abn), Mismatch Repair Deficient (MMRd), mutated E polymerase (POLEmut) and non-specific molecular profile (NSMP). The integration of molecular classification in EC Risk classes has offered the possibility to improve the risk stratification and management of EC to choose patients eligible for adjuvant therapy or to avoid unnecessary treatment in low-risk EC and may low-volume EC disease. The surgical-pathological staging is standard strategy to assess that EC patients need adjuvant therapy, although available data available suggest that molecular classification may play a more accurate prognostic role than histological analysis [51-56]. The available pieces of evidence about the topic are scarce and the existing studies are based on small cohorts. Nevertheless, a usefulness of molecular classification in the prognostic staging of EC was observed in Mueller *et al*. study, despite the small sample analysed [57]. Ongoing studies are assessing the impact of molecular classification in patients with low-volume EC disease and determine factors that predict recurrences in those patients. In 101 patients with EC, molecular analysis was performed

to classified into four molecular classes: POLEmut, MMRd, p53abn and NSMP. Preliminary data show that genomic mutations subclass risk-related can also be found in patients with low-volume metastases in the SNL [58], although their presence is not a predictor of recurrence [59].

CONCLUSIONS

There are still questions regarding the standard retroperitoneal staging method. SLN mapping is optimal method of EC staging with good sensibility, specificity and decreased surgical complications. This, allowing for better surgical staging, provides additional information to direct patients toward tailored treatments to avoid over-treatment and choose suitable patients for adjuvant therapy. The molecular classification offers even more accurate risk stratification and in the coming years it could replace surgical retroperitoneal staging or reserve it only for patients selected according to risk class. In addition, the role of low-volume disease is particularly important for EC patients, especially for low-risk EC because micrometastasis and isolated tumour cells are more likely to be diagnosed at this class of risk than in the high-risk group. Benefits in term of oncological outcome in adjuvant therapy for low-volume disease are controversial and, in the future, the molecular analysis could help us clarify these points [60]. Future research is needed to define which patients may benefit from SLN mapping considering molecular classification and whether specific genetic alterations affect nodal assessment and risk of current cancer.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

I.C., L.S., E.D.A., A.C.: Conceptualization, formal analysis, I.C., L.S., A.C., E.D.A, T.G.D.: Data curation. I.C., L.S., A.C., E.D.A., A.T., I.F., I.A., G.D.B., C.D.D.: Funding acquisition, investigation. I.C., L.S., C.D.D.: Methodology. I.C.: Project administration. I.C., L.S., T.G.D.: Resources. L.M., I.C.: Supervision. L.M.: Validation, visualization. I.C., L.S., E.D.A.: Writing – original draft. All authors have read and agreed to the published version of the manuscript.

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Disclosure of interests

The authors declare that they have no conflict of interests.

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