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Review Article

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Sentinel node mapping in endometrial cancer

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ABSTRACT

Nodal status is one of the most important prognostic factors for patients with apparent early stage endometrial cancer. The role of retroperitoneal staging in endometrial cancer is controversial. Nodal status provides useful prognostic data, and allows to tailor the need of postoperative treatments. However, two independent randomized trials showed that the execution of (pelvic) lymphadenectomy increases the risk of having surgery-related complication without improving patients' outcomes. Sentinel node mapping aims to achieve data regarding nodal status without increasing morbidity. Sentinel node mapping is the removal of first (clinically negative) lymph nodes draining the uterus. Several studies suggested that sentinel node mapping is not inferior to lymphadenectomy in identifying patients with nodal disease. More importantly, thorough ultrastaging sentinel node mapping allows the detection of low volume disease (micrometastases and isolated tumor cells), that are not always detectable via conventional pathological examination. Therefore, the adoption of sentinel node mapping guarantees a higher identification of patients with nodal disease than lymphadenectomy. Further evidence is needed to assess the value of various adjuvant strategies in patients with low volume disease and to tailor those treatments also on the basis of the molecular and genomic characterization of endometrial tumors.

Keywords: Uterine Neoplasms; Lymph Nodes

Synopsis
Although the (indirect) therapeutic value of nodal dissection has not yet proved, the presence of nodal involvement has a certain prognostic role in endometrial cancer. Sentinel node mapping is not inferior to conventional lymphadenectomy in identifying patients with stage IIIC disease.

INTRODUCTION

Endometrial cancer is one of the most common gynecological malignancies [1]. In the United States, the estimated incidence of newly diagnosed endometrial cancer is more than 65,000 new cases in the United States, in 2022 [1].

Author Contributions

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Although the high prevalence of endometrial cancer in developed countries, several features related to its management are still unclear [2,3]. In the recent years, a significant improvement has been achieved in the management of early stage and advanced endometrial cancer patients, with significant benefit in terms of reduced morbidity, improved quality of life, and even in survival benefit. The growing adoption of minimally invasive surgery, molecular/genomic profiling, and immune checkpoint inhibitors aims to reduce surgery related morbidity, enhance prognostication, and improve survival outcomes (especially for patients with hypermutated mismatch repair deficiency/microsatellite instability) and ultramutated (polymerase-epsilon [*POLE*] mutated) profile) [4-10]. However, several features of surgical management of endometrial cancer remain undetermined. Surgery is the mainstay of treatment of endometrial cancer [3]. Hysterectomy (with or without bilateral salpingo-oophorectomy) allows the removal of the primary tumor within the uterus. Uterine risk factors (including histology [endometrioid vs. non-endometrioid], International Federation of Obstetrics and Gynecologists [FIGO] stage and grade of differentiation, depth of myometrial invasion, lymphovascular space invasion [LVSI]) are useful in driving the need of postoperative treatments for reducing the risk of recurrence [3-10]. Moreover, lymph node involvement is one of the main factors influencing prognosis [3].

Interestingly, the role of retroperitoneal staging in endometrial cancer patients is still under debate. Since the results of the Gynecologic Oncology Group (GOG) study in 1987, highlighting the importance of lymphadenectomy in apparent early stage endometrial cancer, accumulating evidence corroborated the importance of nodal status in those patients [11]. In 1988, the FIGO promoted the execution of lymphadenectomy for staging purpose in endometrial cancer patients [12]. Similarly, the American College of Obstetrics and Gynecologists (ACOG) and the National Comprehensive Cancer Network (NCCN) supported the execution of lymphadenectomy for staging purpose in patients affected by endometrial cancer [13,14]. However, the results of two independent randomized trials comparing hysterectomy plus lymphadenectomy vs. hysterectomy alone failed to demonstrate the beneficial effect of adding lymphadenectomy in apparent early stage endometrial cancer. The cumulative results of the Italian trial and the ASTEC trial suggested that the execution of lymphadenectomy does not improve progression free and overall survival, but it increases surgery-related morbidity [15,16]. However, those studies were largely criticized by the presence of several pitfalls in the study design. The main issues are: 1) the large number of patients with low-risk profiles (those with a low risk for nodal involvement); 2) the extent of lymphadenectomy (the low number of nodes yielded in the pelvic area and the low number of patients receiving para-aortic lymphadenectomy); 3) the lack of strict recommendation on the use of adjuvant therapy (that might mitigate the results achieved through lymphadenectomy). The SEPAL study and other well-designed retrospective studies highlighted the importance of the execution of pelvic and para-aortic lymphadenectomy in endometrial cancer patients, especially in those at high risk of having nodal metastases [17]. In the retrospective SEPAL study, combined pelvic and para-aortic lymphadenectomy was associated with a significant improvement of overall survival even in patients receiving adjuvant radiotherapy or chemotherapy [17].

However, only limited evidence is available, and no high-level evidence supported the execution of comprehensive staging in endometrial cancer, even in the intermediate and high-risk groups. Over the last decade, sentinel node mapping emerged as a suitable alternative to lymphadenectomy. To date, sentinel node mapping replaced lymphadenectomy being the mainstay of treatment for retroperitoneal staging purposes in women with uterine

cancer. In the present paper we reviewed current evidence on the role of nodal dissection (lymphadenectomy and sentinel node mapping), focusing also on technique for improving detection rates and provided expert opinion on this topic.

BODY OF EVIDENCE

In this paper, we aim to summarize current evidence regarding the role of nodal status in endometrial cancer. We discussed more relevant papers on the role of retroperitoneal dissection in endometrial cancer, focusing much more on the emergent data on the role of sentinel node mapping. PubMed/MEDLINE, Embase, PubMed Central, Scopus, and Web of Science databases, as well as ClinicalTrials.gov were searched review the current evidence as well as further perspective on the role of retroperitoneal staging in endometrial cancer. Several studies assessed the safety and effectiveness of sentinel node mapping [18-34].

1. Studies investigating the accuracy of sentinel node mapping

Most of the studies investigating sentinel node mapping tested the accuracy of the procedures. Those studies investigated sensitivity/specificity and negative predictive value of sentinel node mapping [26,27]. The prospective FIRES and FILM trials showed that the execution of sentinel node mapping correlates with high accuracy, sensitivity and specificity as well as a low negative predictive value [26,27]. Similarly, other retrospective experience supported the execution of sentinel node mapping instead of lymphadenectomy in endometrial cancer patients [18]. Accumulating evidence supported that sentinel node mapping has the same diagnostic value of lymphadenectomy but correlates with a low risk of developing morbidity [18,19,35]. The FIRES trial is a prospective multicenter single arm study that enrolled 385 patients. Among those, 340 had sentinel node mapping plus pelvic lymphadenectomy [26]. Moreover, 196 (58%) had para-aortic node dissection. Successful mapping of at least one sentinel node was achieved in 86% of patients. More importantly, the FIRES trial highlighted the sensitivity in detecting nodal metastases. Overall, 35 out of 36 (97%) patients with nodal metastases were identified through sentinel node mapping [26]. Other retrospective experience corroborated these findings [26].

2. Studies comparing sentinel node mapping and lymphadenectomy

Accumulating (non-randomized) evidence compared outcomes of patients undergoing sentinel node mapping vs. lymphadenectomy [21-23,29,30]. The Mayo Clinic and the Memorial Sloan Kettering Cancer Center provided interesting data comparing detection rate of two different approaches (i.e., lymphadenectomy and sentinel node mapping). Data of these institutions compared detection rate of positive nodes in the low-, intermediate-, and high-risk population [21,22]. Zahl Eriksson et al. reported data of the low-risk group (those with endometrioid histology and myometrial invasion 50%) and high-risk patients (those with non-endometroid histology). The findings of the study supported that sentinel node mapping is able to provide similar detection rate in comparison to lymphadenectomy in intermediate- and high-risk endometrial cancer [21]. The same study group provided evidence supporting the execution of sentinel node mapping even in serous and clear cell endometrial cancer [29]. Schlappe et al. [29], identified charts of 214 patients (118 and 96 undergoing sentinel node mapping and lymphadenectomy, respectively). Although a difference in progression free survival was noted (possibly due to difference in follow-up schedules), the authors observed that overall survival was not compromised by one approach rather than another [29]. Among, node negative patients (n=168) the-adjusted 3-year recurrence

Table 1. Main studies comparing sentinel node mapping vs. lymphadenectomy in high-risk endometrial cancer endometrial cancer

Author	Patients	Study arms	Oncologic outcomes
Zammarrelli et al. [6]	199 uterine carcinosarcoma	99 SNM	3-yrs PFS: 62.9%; OS: 72.1%
		100 LND	3-yrs PFS: 52.3%; OS: 71.6%
Schlappe et al. [36]	176 deep invasive endometrioid EC patients	82 SNM	3-yrs PFS: 78.7%; OS: 91.8%
		94 LND	3-yrs PFS: 77.7%; OS: 77.6%
Schlappe et al. [29]	214 serous and clear cell EC patients	118 SNM	3-yrs PFS: 69%; OS: 88%
		96 LND	3-yrs PFS: 80%; OS: 77%
Bogani et al. [30]	100 high-risk EC patients	50 SNM	PFS: 84%; OS: 88% at 16 mo
		50 SNM plus LND	PFS: 88%; OS: 88% at 18 mo
Holtzman et al. [37]	189 high-risk EC patients	46 SNM	3-yrs PFS: 71.1%; OS: 81.1%
		143 LND	3-yrs PFS: 71.3%; OS: 95.1%

SNM, sentinel node mapping; LND, lymphadenectomy; PFS, progression-free survival; OS, overall survival.

free survival rates were 73% after sentinel node mapping and 91% after lymphadenectomy, respectively. The adjusted 3-year overall rates were 88% and 86%, respectively [29]. The Memorial Sloan Kettering Cancer Center evaluated the value of sentinel node mapping, even in patients with carcinosarcoma [6]. They compared 99 and 100 patients having hysterectomy plus sentinel node mapping and hysterectomy plus lymphadenectomy [6]. Looking at baseline characteristics, the groups were similar (but patients in the sentinel node group were more likely to have minimally invasive surgery) [6]. In this population no difference in progression free survival and overall survival was noted [6]. Especially on the basis of those data, further studies investigating the role of sentinel node mapping in non-endometrioid endometrial cancer patients are needed. Other retrospective experiences corroborated the safety of sentinel node mapping in the general endometrial cancer population (both low risk and high risk) [19,30]. These studies compared outcomes of patients undergoing sentinel node mapping alone, sentinel node mapping plus backup lymphadenectomy, and standard lymphadenectomy [19,30]. Even in patients at high-risk for nodal metastasis (those with FIGO grade 3 endometrioid tumor with deep myometrial invasion [n=83] and non-endometrioid histology [n=113]) the execution of sentinel node mapping alone provided similar outcomes than sentinel node mapping plus backup lymphadenectomy. Interestingly, this study reported that the execution of backup lymphadenectomy allowed to remove adjunctive positive, non-bulky, nodes in about 1 out of 10 patients. However, the removal of adjunctive positive nodes did not correlate with improved outcomes [30]. **Table 1** shows main studies focusing on the high-risk population [6,29,30,36,37].

3. Surgery-related morbidity

Lymphadenectomy (pelvic and para-aortic) is the most challenging part of the surgical management of endometrial cancer patients; while, hysterectomy is considered a relative safe procedure. Lymphadenectomy correlates with in increasing risk of developing short-term (surgery-related) complications and long-term (lymphatic-related) events. Performing pelvic and para-aortic lymphadenectomy takes longer operative time in comparison to hysterectomy. The cumulative results of randomized trials comparing hysterectomy vs. hysterectomy plus lymphadenectomy showed that this latter approach correlated with a high risk of having morbidity [15]. Lymphadenectomy increased the risk of developing surgery-related events but in particular (long-term) lymphatic-specific complications, including lymphorrhea, lymphoedema, and lymphoceles [15,16]. Lymphatic complications might be severe and in some cases life-threatening [15,16,32]. A few studies have demonstrated improved short and long-term safety of sentinel node mapping over lymphadenectomy [26-31]. A recent retrospective study reported 90-day surgery-related outcomes occurring after sentinel node mapping and lymphadenectomy in apparent early-stage endometrial cancer

patients [32]. The results of this study supported that both the adoption of sentinel node instead of lymphadenectomy and the adoption of minimally invasive instead of open surgery correlated with a lower risk of morbidity and lymphatic-specific morbidity [32]. The other variable influencing the risk of having complications is body mass index (BMI) [32].

4. Pathological ultrastaging

One of the most important features related to the adoption of sentinel node mapping is the pathological assessment [33]. An integral part of the sentinel node algorithm is pathological ultrastaging. Ultrastaging of sentinel nodes uses additional serial sectioning of the nodes with review of multiple hematoxylin or eosin staining slides with or without immunohistochemical analysis. Through the implementation of ultrastaging an important number of lesions (not detectable with conventional pathological assessment) are observed. In particular ultrastaging is able to improve the diagnosis of low volume disease: +50% in the detection of micrometastasis (lesions >0.2 mm and less or equal to 2 mm) and almost 100% in the detection of isolated tumor cells (cells or clusters less or equal to 0.2 mm) [33]. Several studies highlighted that thank to the implementation of ultrastaging we assisted to an increase of patients detected with low volume nodal disease [26-31]. Immunohistochemistry and one-step nucleic acid amplification assay are two effective methods for detecting low volume disease [26-34]. Recently, a prospective study investigated the value of adopting one-step nucleic acid amplification assay for detecting lymph node metastases in uterine malignancies (cervical and endometrial cancers) [34]. This study suggested that one-step nucleic acid amplification assay is a safe and effective in providing rapid results about nodal status, that might be available even at the time of surgery [34]. However, since no data supported the execution of full lymphadenectomy in patients with positive sentinel nodes, having intra-operative details about nodal status would not be something game-changer in the surgical management of endometrial cancer patients. No clear evidence investigated costs of adopting conventional ultrastaging or one-step nucleic acid amplification assay in the field of endometrial cancer. Further evidence is needed to identify cost-effectiveness of these procedures.

5. Low volume disease

Few studies investigated the prognostic value of low volume disease, reporting that the presence of micrometastasis and isolated tumor cells influence patients' outcomes. However, no consensus regarding the optimal treatment modality still exists. In fact, only few studies reported outcomes of patients with low volume disease who are not treated with adjuvant therapies [28,33]. Ghoniem et al. [31] reported the results of an international multi-institutional retrospective study, investigating oncologic outcomes in endometrial cancer patients with low volume disease. In this large experience, 247 patients were evaluated (132 and 115 with isolated tumor cells and micrometastasis, respectively). The authors observed that the main risk factors for recurrence are: 1) non-endometroid histology; 2) LVSI; and 3) uterine serous invasion [33]. The authors concluded that patients with endometrioid FIGO grade 1 tumors and isolated tumor cells, but without LVSI and uterine serous invasion are characterized by a favorable prognosis, even when untreated [33]. However, only 18 patients had these characteristics. Hence, further trials are needed to test the most appropriate approach in endometrial cancer patients with low volume disease [33].

6. Technical consideration for improving detection rates

All those data supported the value of adding sentinel node mapping in endometrial cancer. Owing its importance, it is paramount to perform an accurate bilateral mapping. International guidelines supported the adoption of sentinel node mapping [33,38]. According to the current

NCCN guidelines, the adoption of sentinel node mapping includes the execution of side specific lymphadenectomy in case of mapping failure [12]. Para-aortic lymphadenectomy can be considered on the basis of surgeons' discretion. According to available data, mapping failure (at least one pelvic side) occurred in about 10%–15% of patients [26]. Since sentinel node mapping is a win to win scenario (it improves detection of positive nodes in comparison to lymphadenectomy without increase morbidity), several studies investigated strategies for improving detection rate, thus reducing the need of the execution of side-specific lymphadenectomy [38]. Most of those studies focused on investigating different tracers and different site of injection. Below are described the finding of the most representative studies on these issues [35,39-42]. Over the last decade, several tracers have been adopted for the identification of sentinel node during mapping procedures [35,39-42]. Historically, radioisotope and blue dye were used for sentinel node mapping procedures [35]. Technetium 99 (Tc99) has been adopted also for mapping the lymphatic drainage of other tumors, including vulvar cancer and breast cancer. The adoption of Tc99 was useful especially for those cases performed via open surgery. Blue dye can be used much more easily since it can be injected directly at the time of surgery; while Tc99 have to be injected before surgery and in general its use requires a coordination between different units (i.e., nuclear medicine and gynecology) [35]. To date, the most adopted tracers in clinical practice is indocyanine green (IGC). Accumulating evidence supported that the adoption of IGC in combination with near infrared technology provides excellent results in term of detection rate [27,35]. The prospective phase III multi-institutional FILM trial compared the use of different tracers in patients with uterine malignancies (including cervical and endometrial cancers) [27]. In this study, patients were randomized to have injection of blue dye followed by IGC and IGC followed by blue dye. This study supported the adoption of IGC since this tracer allowed to identify more nodes in comparison to the blue dye. A recently published Cochrane review on this issue reported that the sensitivity of IGC alone was 92.5% (95% confidence interval=81.8–97.1) [35]. However, a meta-regression on various studies showed that sensitivities are similar between various tracers and combination of tracers [35]. Another topic deserving attention is the most appropriate site of tracers' injection [18,33,42,43]. Cervical injection (at 3 and 9 o'clock) is the most used injection site because of the high reproducibility of the procedure. Other popular injection technique included the execution of fundal and hysteroscopic injections [18,42,43]. Fundal injection failed to demonstrated a benefit in sentinel node mapping identification. The main reasons is that this type of technique is skipping the drainage within the parametria and more importantly the majority of endometrial tumors are not invading the serosal [43]. Following a logical assumption peri-tumoral injection, via hysteroscopy, would provide a more accurate detection of the real nodes draining the tumor. In fact, the lymphatic drainage of the uterus is complex and not only through the lymphatic vessels close the uterine vessels and the parametrium. In comparison to cervical injection, hysteroscopic one is more likely to detect para-aortic sentinel nodes, allowing to identify the lymphatic drainage through the ovarian vessels (especially for tumors growing in the uterine fundus only). However, we have to point out that anatomical studies suggested that fundal tumors are not frequent [18]. Few studies reported excellent detection rate both in the pelvic and para-aortic area after the execution of hysteroscopic-guided peri-tumoral injection [18]. To identify the optimal site of injection the MITO study group performed a randomized study comparing cervical and hysteroscopic injection [18]. Patients with stage I and II endometrial cancer were randomized to have hysteroscopic (n=69) and cervical (n=82) injection. The study population included about 88% and 12% of patients with endometrioid and non-endometroid endometrial cancer, respectively [18]. Cervical invasion was noted in 6.6% of patients [18]. Hysteroscopic injection correlated with a 10% increase in para-aortic detection rate. More importantly, hysteroscopic injection

was able to increase detection rate of isolated positive para-aortic nodes in comparison to cervical injection (5.8% vs. 0%). However, pelvic and overall sentinel node detection rates were higher with cervical injection instead of hysteroscopic injection [18]. To date, the execution of cervical injection with IGC is considered the most safe and accurate procedure for sentinel node mapping in endometrial cancer patients. This procedure is easily performed, and it is not time consuming. Cervical re-injection of IGC might be useful in reducing the burden of mapping failure and improving detection rate of sentinel nodes [44]. Maramai et al. [44], reported data about a retrospective study involving 251 endometrial cancer patients. Unilateral and bilateral detection was 22.7% and 73.3% at the time of injection one, respectively. In 4% of patients, sentinel nodes were not detected. Among the 67 patients without bilateral sentinel node detection, 51 were re-injected. After re-injection, bilateral and unilateral detection rate was 94.5% and 5.1%, respectively. In 0.4% (n=1) of patients, sentinel nodes were not detected [44]. Those data highlighted that re-injection was a feasible method to improve detection rates of sentinel nodes. Further evidence is needed to identify factors influencing detection rates and to improve the correct identification of the first nodes draining the tumor.

DISCUSSION

Several studies supported the feasibility of implementing sentinel node mapping in apparent early-stage endometrial cancer [18-34,38-45]. However, it is important to point out that the quality of evidence is still scant, since no data from a phase III randomized trial are available. Ongoing studies will clarify the role of adding sentinel node mapping to hysterectomy for endometrial cancer staging [46]. In particular, the ALICE trial and the ENDO-3 trial aim to evaluate sentinel node mapping vs. lymphadenectomy and vs. no nodal staging, respectively [47,48]. On the basis of the available evidence the incorporation of sentinel node mapping algorithm is able to improve the detection rate of nodal metastases in endometrial cancer patients. The execution of sentinel node mapping during minimally invasive procedures (through the incorporation of near infrared technology) represent a win to win scenario. Level A evidence supported the safety of minimally invasive surgery [38]. In comparison with open surgery, minimally invasive surgery (i.e., laparoscopic and robotic-assisted surgery) correlates with similar long-term oncologic outcomes, improving the short-term postoperative course. Moreover, growing evidence suggested the safety of sentinel node mapping performed via minimally invasive approach [45,49]. Sentinel node mapping is not inferior to conventional lymphadenectomy in detecting patients harboring with nodal disease (some micrometastases and all macrometastases). Through ultrastaging (extensive pathological evaluation of the nodes), sentinel node mapping is able to identify nodal disease not detectable via conventional pathological evaluation (some micrometastases and all isolated tumor cells). Additionally, growing evidence suggested that the adoption of sentinel node mapping does not impact on surgery related outcomes (in terms of operative time, estimated blood loss, and morbidity) [49]. A recent retrospective study performed by our study group compared outcomes of patients undergoing hysterectomy plus sentinel node mapping versus hysterectomy alone [49]. Using a propensity score matching, outcomes of 150 patients having hysterectomy versus 150 patients having hysterectomy plus sentinel node mapping were compared. Overall, severe complication rates were similar between groups (0.7% following hysterectomy vs. 1.3% following hysterectomy plus sentinel node mapping). No lymphatic-specific complication occurred. These data supported the safety of adopting sentinel node mapping [49]. For all these reasons sentinel node mapping has to be implemented. Avoiding mapping failure and the need of performing side specific

lymphadenectomy is an unmet need in the management of apparent early-stage endometrial cancer. The missed opportunity to retrieve sentinel node would increase complication rates (due to the execution of lymphadenectomy) and reduce detection rates of positive nodes (since the lack of adopting ultrastaging). Using cervical injection of IGC (and eventually re-injection) in combination with near infrared technology seems to most appropriate method to improve detection rate of sentinel nodes [44]. Since the visualization of IGC depend only by near infrared technology, the adoption of IGC is not impacting surgical field visualization (while it might occur with blue dye). Minimally invasive surgery is the most appropriate route for identifying sentinel nodes both for the incorporation of the near infrared technology and the magnified view [36,37,50-52]. Surgical exploration of the retroperitoneal are should be performed carefully and gently in order to avoid damages of the lymphatic channels. Although several data supported the value of performing sentinel node mapping, the role of low volume disease is still uncertain. Accumulating evidence suggested that isolated tumor cells and micrometastases provide useful information for assessing patients' prognosis. However, the role of adjuvant therapy in these patients is still unclear. No data clearly showed a benefit to add adjuvant treatments, especially in case of isolated tumor cells. Several authors auspicated that the introduction of molecular and genomic profiling would be useful for clarify the role of low volume disease. Potentially low volume disease in patients with *POLE* mutation might be omitted; while would be necessary in patients characterized by *TP53* mutation [49]. However, limited experience trying to correlate low volume disease with molecular and genomic profile, failed to demonstrate an impact of this latter on outcomes of patients with low volume disease [51]. Of note, only 17 patients were included in the "ultra-mutated" group of the TGCA study [38]. This data strongly highlight that we cannot draw any conclusion on the role of nodal disease (either for isolated tumor cells, micrometastasis, or macrometastasis) in patients with *POLE* mutation. Further data are needed, since the level of evidence is scant. No solid evidence is still correlating conventional risk factors with molecular and genomic characterization of endometrial tumors. Endometrial tumors are characterized by a high level of heterogenicity, thus would not be possible to identify a single (worthy) approach for every patient. Improving detection of positive nodes is of paramount importance [53]. Detecting positive nodes would be useful for assessing patients' prognosis and to tailor the need of adjuvant treatments. Adopting sentinel node mapping we increased our ability to detect disease harboring in the lymph nodes. Although further evidence is necessary to assess the role of low volume disease, even detecting isolated tumor cells seems provide useful data for providing the best adjuvant strategy in endometrial cancer patients. Further studies are warranted. In fact, new evidence is needed to provide the real value of nodal disease and molecular/genomic characterization in endometrial cancer. Reducing invasiveness and unnecessary treatments would improve 356 patients outcomes, including their quality of life. More interestingly, another randomized trial comparing the 357 execution of sentinel node mapping versus no nodal staging would be necessary to assess the real pros and 358 cons of adding sentinel node mapping during our staging procedures.

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