

Lymphadenectomy in endometrial cancer: for and against

Interview with C. Marth¹ and P. Benedetti Panici² by C. Marchetti² and A. Musella²

In favour of lymphadenectomy:

C. Marth¹

Against lymphadenectomy:

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Introduction

Endometrial cancer (EC) is the most common malignancy of the female reproductive tract and is increasing in incidence. The treatment of EC has changed substantially over recent decades with the introduction of a new staging system and surgical approaches accompanied by novel adjuvant therapies. Primary surgical treatment is the mainstay of therapy; nonetheless a consensus regarding the role and extent of lymphadenectomy in endometrial cancer has not yet been reached. Non-surgical treatment, traditionally based on radiotherapy, has also evolved and chemotherapy has been incorporated into treatment strategies, either alone or combined with radiation.

We have interviewed two experts on this topic to try and clarify the pros and cons, and risks and benefits of lymphadenectomy in endometrial cancer using an evidence-based approach.

1. Lymphadenectomy in endometrial cancer (EC): does it have a role in surgical staging or/and in tailoring adjuvant treatment?

Pro lymphadenectomy

Lymphadenectomy is an integral part of the comprehensive surgical staging of EC. However, the role of lymph-

adenectomy in early EC remains controversial. The shift to surgical staging was due, in part, to the results of GOG 33 [1]. All 621 patients in this trial underwent a standard comprehensive staging procedure, including hysterectomy, bilateral salpingo-oophorectomy, collection of pelvic washings, and a selected pelvic and para-aortic lymph node dissection. Pathologic factors were examined to determine risk of extrauterine involvement and lymph node metastasis. Based on multivariate analysis, three risk categories were defined. Patients with low-risk disease had no pelvic or para-aortic lymph node metastasis. Those with moderate-risk disease had an incidence of pelvic and para-aortic lymph node metastasis of 18% and 15%, respectively. Patients with intraperitoneal disease and only 50% myometrial involvement had a 33% risk of pelvic lymph node metastasis and an 8% risk of positive para-aortic lymph nodes. Patients with both high-risk criteria were at the highest risk, with rates of pelvic lymph node metastasis and para-aortic lymph node involvement of 61% and 30%, respectively [2].

The advantages of comprehensive surgical staging lie in diagnosis, prognosis, and proper triage of patients for adjuvant therapy. Several observational studies have compared outcomes in early-stage EC patients with and without systematic lymphadenectomy [3-10]. A large series utilising a national database supports lymph node dissection for grade 3 tumors only. This was also the finding of an observational study that examined patients with intermediate or high risk factors for recurrence who underwent surgery with pelvic lymphadenectomy with or without para-aortic lymph node dissection. There was a survival benefit for those who had a para-aortic lymphadenectomy compared with those who did not, but not in patients with low-risk cancers [11].

Other studies suggest that the benefit obtained with lymphadenectomy depends on the number of lymph nodes removed at the time of surgery. However, there are no randomised trials supporting the benefit of lymphadenectomy in early-stage endometrial cancer. There are two randomised trials that provide evidence against surgical staging [12, 13]. Benedetti Panici and colleagues randomised 514 women with clinical stage I EC to either systematic

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pelvic lymphadenectomy or no lymph node dissection and found no improvement in disease-free or overall survival (OS) between the two groups [12]. The Adjuvant External Beam Radiotherapy in the Treatment of Endometrial Cancer (ASTECC) trial, randomised 1408 women with clinical stage I EC to staging surgery with or without pelvic lymphadenectomy [13]. Those women with early-stage disease with intermediate or high risk factors for recurrence were then randomised, independent of lymph node status, to the ASTEC radiotherapy trial. This study found no difference in progression-free survival (PFS) or OS and recommended against routine pelvic lymphadenectomy in presumed early-stage EC.

One benefit of nodal dissection is triage to adjuvant therapy. However, the clinical value of triage to treatment in the ASTEC trial was obscured because only half of the patients with high-risk disease were randomised to adjuvant therapy. The ASTEC trial also does not provide information about the usefulness of pelvic lymphadenectomy for guiding adjuvant treatment because patients were secondarily randomised to radiotherapy without factoring in lymph node status. In addition, the benefit of para-aortic lymph node dissection is not addressed because patients underwent para-aortic node palpation and selective sampling rather than systemic dissection.

Against lymphadenectomy

The role of lymphadenectomy in EC treatment is still debated and an unusual divergence exists between evidence-based medicine and current clinical practice. Strong evidence from randomised controlled trials have provided guidance against the use of surgical staging. In Italy, my group performed a randomised controlled trial in enrolling 514 women with clinical stage I EC who received either systematic pelvic lymphadenectomy or no lymph node dissection [12]. Pelvic systematic lymph node dissection was defined “adequate” when ≥ 20 pelvic lymph nodes were removed and analysed by the pathologist. We found no statistically significant differences in disease-free survival and OS between the lymphadenectomy and no lymph node dissection groups [12]. Furthermore, there was no statistically significant difference in recurrence pattern between the two groups, regardless of nodal involvement; lung, intraperitoneal and vagina were the most common sites of recurrence.

This study was followed by the ASTEC trial, a large, multi-centre, European trial that randomised 1408 women with clinical stage I EC to staging surgery with or without pelvic lymphadenectomy [13]. Women with early-stage disease with intermediate or high risk factors for recurrence were then randomised, independently of lymph node status, to the

ASTECC radiotherapy trial. This trial did not find any difference in PFS and OS between the groups, and recommended against routine pelvic lymphadenectomy in presumed early-stage EC.

These results have been criticised in light of several non-randomised studies. One of these demonstrated, on the basis of a retrospective analysis, that pelvic and para-aortic lymphadenectomy was associated with longer OS for patients with intermediate- or high-risk EC [14, 15]. Also several biases have been proposed, such as the “selective” rather than “systematic” lymphadenectomy procedure in the ASTEC trial, as well as the non-homogeneous administration of adjuvant therapy in the Italian trial. Nonetheless, up to now, no randomised trials in favour of lymphadenectomy have been published and, overall, the available evidence is not strong enough to establish that lymphadenectomy has either a surgical or therapeutic role in low risk EC.

In the absence of any hard evidence, it is also important to remember that the majority of EC patients are old, obese and have cardiovascular or metabolic comorbidities that increase the risk of peri-operative complications. Therefore, it is important to tailor the extent and radicalness of surgery in order to decrease morbidity and mortality potentially associated with unnecessary procedures. Specifically, women with negative nodes derive no benefit from unnecessary lymphadenectomy, but may develop short- and long-term morbidity related to this procedure, especially lymphedema that was reported in 13% of patients who underwent lymphadenectomy in one trial [16]. A subsequent analysis of the Italian randomised study [17] has showed that older women (>65 years) receiving lymphadenectomy had a poorer survival, with no difference in OS and CSS between node-negative and node-positive patients.

2. Pelvic and para-aortic lymphadenectomy: what are the possible acceptable indications and how radical it should be? 62012 phase III trial?

Pro lymphadenectomy

Based on International Federation of Obstetricians and Gynaecologists (FIGO) staging guidelines, clinically early-stage EC patients should undergo comprehensive surgical staging. However, the disadvantages of surgical staging may outweigh the risks in patients with low-grade endometrial tumors. In this subset of patients, intraoperative frozen pathology may be used as a method of triaging patients to lymphadenectomy. In higher risk disease, the benefits of complete surgical staging outweigh any potential disadvantages of lymphadenectomy.

The definition of an adequate lymphadenectomy has not been standardised: current approaches include pelvic lymphadenectomy, para-aortic lymphadenectomy to the inferior mesenteric artery and para-aortic lymphadenectomy up to the renal vessels. In addition, the recommended number of lymph nodes to remove has not been defined.

Sampling of lymph nodes has a low sensitivity in EC. Indeed, it has been shown that para-aortic nodes may be positive in the absence of positive pelvic nodes, suggesting that para-aortic lymph nodes should be removed in cases where a lymphadenectomy is indicated. In the Mayo Clinic experience of 281 patients with EC who underwent lymphadenectomy, 51% had both positive pelvic and para-aortic nodes, 33% had positive pelvic lymph nodes only, and 16% had isolated para-aortic lymphadenopathy [18]. Due to the fact that the majority of patients (77%) with para-aortic lymph node involvement had metastases above the inferior mesenteric artery [18], para-aortic lymphadenectomy up to the renal vessels is recommended. If a lymphadenectomy is performed, systematic removal of pelvic and para-aortic nodes up to the level of renal veins should be considered.

Against lymphadenectomy

We know that the expected rate of para-aortic involvement in the presence of metastatic pelvic lymph nodes can be as high as 30-50% [19]. To date, the only evidence favouring para-aortic lymphadenectomy in terms of OS come from a retrospective analysis [14]. In our randomised trial, the extent of lymphadenectomy did not systematically include para-aortic lymph nodes [12]; nonetheless, in accordance with the literature, we found that five out of 16 patients with pelvic node involvement who underwent extended lymphadenectomy had also aortic involvement. Of note was that only four patients relapsed at the overall lymph node level in each arm (and only one at aortic level in each arm), thus demonstrating no significant correlation.

Interestingly, in retrospective series favouring para-aortic lymphadenectomy, improved outcomes were limited to patients at highest risk (defined as high grade, type II histology, lymphovascular space involvement [LVSI], >50% myometrial invasion, or FIGO stage III/IV), supporting findings that the majority of patients with endometrioid EC may potentially forgo a lymphadenectomy procedure, with associated reductions in surgical morbidity and cost. However, a prospective randomised study should validate the therapeutic effect of aortic and pelvic lymphadenectomy before considering these data as applicable to clinical practice.

How radical the procedure should be remains controversial, reflecting a lack of standardisation of lymphadenectomy technique. Nonetheless, it has been demonstrated that metastases above the inferior mesenteric artery are

present in 77% of patients with para-aortic node involvement [18]. Therefore, when a lymphadenectomy is planned, para-aortic lymphadenectomy up to the renal vessels is preferable [20-23].

3. Do you believe that sentinel lymph node mapping might have a role in the surgical management of EC?

Pro lymphadenectomy

Sentinel lymph node dissection (SLND) could represent a compromise between no dissection (leaving a small proportion of node-positive patients) and full dissection (adding a useless procedure for the majority of node-negative patients). In addition, ultrastaging of the sentinel lymph nodes (SLNs) using intracervical injection of dye and colloid detects micrometastases otherwise undiagnosed by conventional histology, even in patients considered at low risk. The question of alternative injection sites in the endometrium or uterine fundus, which are anatomically more logical, is still a topic for investigation. Injection under hysteroscopic, ultrasound, laparoscopic or open guidance in patients with EC has been addressed, without evidence of benefit of the more demanding and less practical modalities. Nevertheless, evidence is accumulating that SLND may be useful in the management of endometrial cancers.

Against lymphadenectomy

SLN assessment, which is the standard of care in malignancies such as breast cancer and melanoma, is now being introduced in gynaecologic cancers. The role of SLN mapping in the treatment of EC treatment is still under investigation. Available data from the prospective multicenter SENTI-ENDO study suggesting that SLN biopsy has a sensitivity of 84% in FIGO stage I and II EC patients [24]. The long-term results of this study demonstrated that 18/125 patients (14.4%) experienced a recurrence. The 50-month recurrence-free survival (RFS) rate was 84.7%, with no difference between patients with and without detected SLN ($p=0.09$). Among patients with detected SLN ($n=111$), no difference in relapse-free survival was observed between those with and without positive SLN ($p=0.5$). This probably means that ultra-staging of the SLN may be more sensitive than a full lymphadenectomy but we still do not know the clinical importance of isolated tumor cells discovered in a lymph node. This also means that further studies focusing on the management of EC should take into account not only the extent of lymphadenectomy or the interpretation of SLN biopsy results but also, and especially, the chance of stratifying adjuvant therapies according to lymph node/SLN status. In our ini-

tial experience with 30 patients affected by stage I-II EC and submitted to sentinel node mapping, two cases (7%) presented with sentinel-node neoplastic involvement at histologic examination (unpublished data).

4. In your opinion, is lymphadenectomy cost-effective? How does it impact on morbidity and quality of life?

Pro lymphadenectomy

The cost-effectiveness of various strategies for lymphadenectomy is controversial. Clements et al. [25] demonstrated that a strategy of selective lymphadenectomy based on intraoperative risk factors was less cost-effective than routine lymphadenectomy. In addition, Cohn et al. [26] suggested that surgical staging for all patients was the most cost-effective strategy compared with no staging and staging based on frozen sections following hysterectomy. However, a prospective study [18] has shown that lymphadenectomy increased morbidity and the cost of care without increasing survival rates in patients with low-risk EC as defined by Mayo Clinic criteria: type I histology, grade 1 or 2, myometrial invasion $\leq 50\%$, and tumor diameter ≤ 2 cm.

With lymph node dissection, concerns include the prolongation of operating time and increased morbidity, especially if more extensive surgery is combined with external-beam radiation therapy or chemotherapy. Chronic morbidity directly related to lymphadenectomy, such as leg oedema, occurs in at least 5% of patients. Para-aortic lymphadenectomy further increases the risk of major complications, but might also identify patients requiring extended-field radiotherapy. A major controversy remains as to whether lymphadenectomy is purely diagnostic or if it is therapeutic, and if radiation therapy could be omitted for all node-negative patients with high risk factors because data for this setting of patients are still unclear [27].

The role of lymphadenectomy is a topic of ongoing debate, and the selection of patients for lymphadenectomy, the extent of lymphadenectomy (pelvic and/or aortic), and whether a minimum number of nodes should be required to consider lymphadenectomy adequate are unresolved issues, and data from randomised studies are lacking.

Against lymphadenectomy

Several authors have noted that patients receiving systematic pelvic and para-aortic lymphadenectomy experience longer operative times and are exposed to a higher risk of intraoperative and postoperative complications than pa-

tients who have hysterectomy and bilateral salpingo-oophorectomy alone. In our study [12] we found that both early and late postoperative complications occurred significantly more frequently in patients who had received pelvic systematic lymphadenectomy (81 patients in the lymphadenectomy arm and 34 patients in the no-lymphadenectomy arm, $p=0.001$). Similar results were reported in the ASTEC trial [13]. Longer hospital stay due to side effects as well as management of these complications imply a significant increase in costs. Furthermore, as mentioned above, EC patients often present with several comorbidities and are at higher risk of surgical perioperative complications. Interestingly, a prospective study from the Mayo Clinic has shown that lymphadenectomy increased morbidity and the cost of care without increasing survival rates in patients with early-stage low-risk endometrial cancer (as defined by Mayo Clinic criteria) [28]. Of course, should be mentioned that both trials were performed in the era of open surgery and that it would be reasonable to assume that the advent of minimally invasive surgery would have decreased both complications and hospital stay. Nonetheless, in our opinion, while it is not possible to demonstrate any survival advantage for patients who undergo pelvic and/or aortic lymphadenectomy, a cost-effective option could be removal of nodes detected as bulky at preoperative imaging because these enlarged nodes are known to have a low response rate to chemotherapy or radiotherapy.

5. What are the prerequisites for deciding who requires adjuvant treatment? And, do you have a standard of treatment for these patients?

Pro lymphadenectomy

The most important prognostic factors for tailoring adjuvant therapy include FIGO stage, lymph node involvement, histologic type, grading, myometrial invasion and LVsI. More recently, other factors derived from molecular analysis have made an important contribution to predicting which patients are in the high-risk group. POLE proofreading mutations predict favourable EC prognosis, especially in high-grade tumors. The expression of the adhesion molecule L1CAM has been shown to be the best-ever published prognostic factor in FIGO stage I, type I endometrial cancers and shows clear superiority over the standard and widely-used multifactor risk score [29]. L1CAM expression in type I cancers indicates the need for adjuvant treatment and might serve as a treatment target for the fully humanized anti-L1CAM antibody currently under development for clinical use.

For stage I and II endometrioid cancers, adjuvant therapy has shown no OS benefit. Brachytherapy improves vaginal control and external beam radiotherapy improves vaginal and pelvic control. Adjuvant chemotherapy is of unproven benefit. For stage III EC, chemotherapy is recommended to improve PFS and CSS. External beam radiation therapy (EBRT) is recommended to decrease pelvic recurrence, with improvements in PFS and OS. There is more evidence for the use of chemotherapy and EBRT in combination for stage III patients than either approach alone.

Against lymphadenectomy

The role of postoperative treatments in early-stage EC is controversial. Recently, a Cochrane meta-analysis on adjuvant radiotherapy for stage I EC concluded that EBRT reduces the risk of loco-regional recurrence but does not provide any significant advantage with respect to CSS or OS. Furthermore, EBRT is associated with significant morbidity and a reduction in quality of life, and may have an adverse effect on EC survival when used to treat uncomplicated low-risk (stage IA-B grade 1-2) patients [30]. Conversely, chemotherapy has shown to be more beneficial for distant disease control than for loco-regional relapse [31], but the impact on survival doesn't change. Interestingly, the authors reported that chemotherapy was not significantly better than abdominal radiation in patients with non-endometrioid tumors. Similarly, the results of two randomised studies (NGSO/ERTC and MANGO ILIAD-III), including high-risk EC patients (FIGO stage I to III), indicated that the addition of adjuvant chemotherapy to radiation improved disease-free survival overall, especially in the subgroup with grade 1-2 endometrioid EC, without benefits in patients with endometrioid grade 3 and type II EC. Therefore, adjuvant therapy should be carefully tailored for individual patients.

In our opinion, the urgent question to be addressed should no longer be "lymphadenectomy, yes or no" nor "which adjuvant therapy for positive nodes" but instead focussed on the identification of clinical and biomolecular factors (other than nodal status, myometrial invasion, histological type and LVsI) which might be indicative of tumor aggressiveness. Among clinical factors, we have recently demonstrated that, beyond histotype, both age >65 years and body mass index (BMI) >30 kg/m² are significantly corre-

lated with poor prognosis, regardless of lymph nodal status [17]. These patients are perhaps those who may benefit from adjuvant therapy. In contrast, BMI, lymph node status and use of adjuvant therapy did not influence outcomes in younger patients.

To date, there are no reliable markers to identify high-risk patients or those needing strict follow-up, with or without adjuvant treatments. In our opinion, an accurate analysis of biomolecular patterns of cancers occurring in these subgroups of women age is mandatory, with the aim of identifying new effective cancer-tailored adjuvant treatments.

6. What is the standard of care for EC patients in your referral centre?

Pro lymphadenectomy

Surgery is still the most important part of EC treatment. In the majority of patients we perform laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Pelvic and para-aortic lymphadenectomy is indicated in patients with one of the following risk factors: >50% myometrial invasion, grade 3, LVsI, non-endometrioid histology. More recently L1CAM-positive patients have also been included.

Vaginal brachytherapy is indicated in all patients with non-endometrioid histology or grade 3 or >50% myometrial invasion or LVsI positive. Adjuvant chemotherapy is standard for all patients with FIGO III and endometrioid histology. Chemotherapy is also considered for earlier stages in other histologic types.

Against lymphadenectomy

Surgery, including total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO), is the most important part of EC treatment. For the majority of patients without high-risk factors we perform laparoscopic-assisted vaginal hysterectomy (LAVH) with bilateral salpingo-oophorectomy. Lymphadenectomy is performed to remove bulky nodes detected at preoperative instrumental imaging (positron emission tomography-computed tomography [PET-CT]), or to remove nodes detected at sentinel node mapping. The treatment algorithm followed in our Institution is detailed in Figure 1.

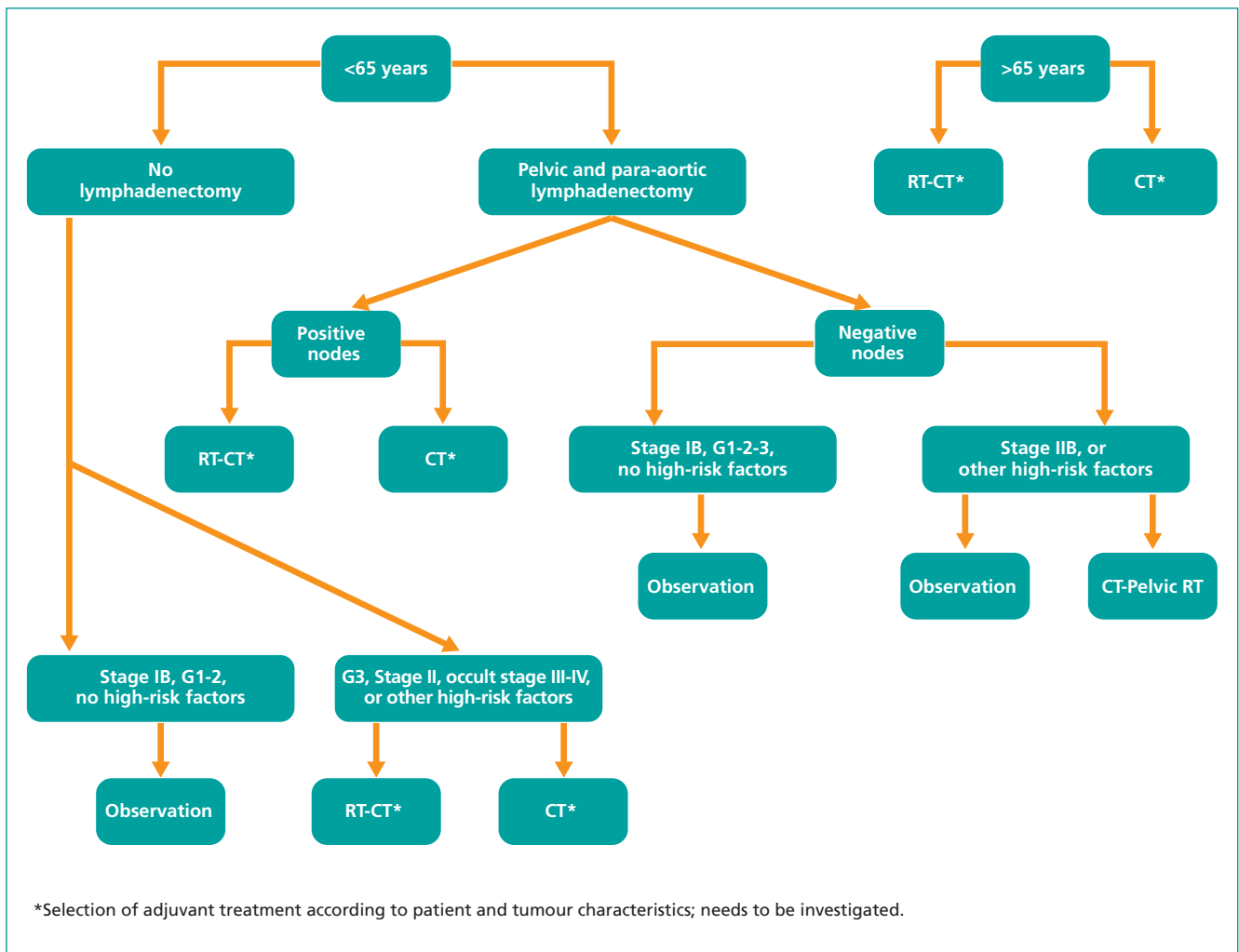


Fig. 1. Endometrial cancer: Sapienza Institution treatment algorithm. CT: chemotherapy; RT: radiotherapy.

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