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Surgical Management of Early Endometrial Cancer: An Update and Proposal of a Therapeutic Algorithm

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In the last few years technical improvements have produced a dramatic shift from traditional open surgery towards a minimally invasive approach for the management of early endometrial cancer. Advancement in minimally invasive surgical approaches has allowed extensive staging procedures to be performed with significantly reduced patient morbidity. Debate is ongoing regarding the choice of a minimally invasive approach that has the most effective benefit for the patients, the surgeon, and the healthcare system as a whole.

Surgical treatment of women with presumed early endometrial cancer should take into account the features of endometrial disease and the general surgical risk of the patient. Women with endometrial cancer are often aged, obese, and with cardiovascular and metabolic comorbidities that increase the risk of peri-operative complications, so it is important to tailor the extent and the radicalness of surgery in order to decrease morbidity and mortality potentially derivable from unnecessary procedures. In this regard women with negative nodes derive no benefit from unnecessary lymphadenectomy, but may develop short- and long-term morbidity related to this procedure. Preoperative and intraoperative techniques could be critical tools for tailoring the extent and the radicalness of surgery in the management of women with presumed early endometrial cancer. In this review we will discuss updates in surgical management of early endometrial cancer and also the role of preoperative and intraoperative evaluation of lymph node status in influencing surgical options, with the aim of proposing a management algorithm based on the literature and our experience.

MeSH Keywords: **Algorithms • Endometrial Neoplasms – therapy • Gynecologic Surgical Procedures – utilization**

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Background

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries.

Abnormal uterine bleeding after menopause is the most frequent and early symptom of EC, which is usually a uterine-confined disease with favorable prognosis in most patients.

The main disputes concern the management of patients with early endometrial cancer (EEC), particularly the question of which is the optimal surgical approach: laparotomy, standard laparoscopy, robotic surgery, mini- and micro-laparoscopy, laparo-endoscopic single-site surgery, or robotic single-site surgery. Another question is whether lymphadenectomy is the optimal surgical technique.

As clinical and instrumental preoperative staging of EC is associated with underestimation of disease for 13–22% of patients, routine surgical staging has been recommended by the International Federation of Gynecology and Obstetrics (FIGO) since 1988 [1].

A complete surgical staging for EC includes the collection of peritoneal fluid by washing, exploration of the peritoneal cavity, selective biopsies of suspicious areas, extrafascial total hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymphadenectomy [2,3].

Women with EC are often aged and obese and have cardiovascular and metabolic comorbidities that increase the risk of peri-operative complications. Therefore, it is important to tailor the extent of surgery to decrease morbidity and mortality potentially associated with unnecessary procedures. For these reasons, it could be helpful to construct an algorithm to standardize the management of EEC and improve the comparability of the results obtained. To achieve this goal, the focus of this article is to review updates in surgical management of EEC.

Preoperative and intraoperative techniques could be critical tools for tailoring the extent and the radicalness of surgery in the management of women with presumed EEC. In this review we discuss also the role of preoperative and intraoperative evaluation of lymph node status in influencing surgical options, and we propose a management algorithm based on the literature and our experience.

Search Strategy and Selection Criteria

Data for this review were identified by a PUBMED search using the search terms “endometrial cancer”, “management”, “surgery”, “lymphadenectomy”, “imaging”, “serum markers”,

“frozen section”, and “sentinel-node”. In addition, references from relevant articles were searched to identify additional relevant studies. Although we limited the main search to publications in English, frequently cited articles in other languages were also included. Although preference was given to prospective studies, several retrospective studies and review articles were also included because they provide comprehensive historical overviews.

Surgical Approach with EEC (Stage I FIGO₂₀₀₉)

Laparoscopic surgery: Standard laparoscopy, laparo-endoscopic single-site surgery, mini- and micro-laparoscopy

Laparotomy has long been the standard approach in patients diagnosed with EEC [2].

Thereafter, laparoscopic approach has overcome limits associated with vaginal surgery in the treatment of patients with EEC. The main limits of a vaginal approach are due to the difficulty in performing the salpingo-oophorectomy and the impossibility to carry out abdominal and retroperitoneal exploration, peritoneal cytology and lymphadenectomy, and therefore to perform a complete anatomical-surgical staging [4].

The Gynecologic Oncology Group (GOG) published the results of the largest randomized trial (LAP2) comparing laparoscopy to laparotomy in the surgical staging of women with EEC (Table 1). In the GOG LAP2 study, laparoscopy provided equivalent results in terms of survival compared with laparotomy, with further benefits: lower morbidity in obese women, decreased estimated blood loss, equivalent or superior ability to retrieve pelvic and para-aortic nodes, less antibiotic use, shorter hospital stay, lower rate of postoperative complications, less use of analgesics, earlier resumption of normal activities, and better body image and quality of life [5–7]. Laparoscopic surgery, done by experienced surgeons, did not give more significant intra-operative complications than open surgery [5,8,9].

To obtain more consistent evidence regarding the effects of laparoscopy in EEC, Wang et al. recently conducted a meta-analysis of randomized trials quantitatively evaluating clinical outcomes including complications and mortality rate [10]. Wang et al. confirmed the results of 2 previous meta-analyses [8,20], showing evidence of a benefit for laparoscopy over laparotomy in the surgical staging of women with EEC (Table 2).

In recent years, the evolution of technology has focused on improving intra- and post-operative performances of standard laparoscopy, and efforts have been made to modify the peritoneal access to further improve post-operative recovery and

Table 1. Results of GOG LAP2.

	Laparotomy	Laparoscopy	p value
Median operative time minutes (IQR)	130 (102–167)	204 (160–252)	<0.001
Intraoperative complications % of patients (bowel, vein, artery, bladder, ureter, etc.)	8	10	0.106
Perioperative and postoperative period % of patients			
Blood transfusion	7	9	0.28
Antibiotics	23	16	<0.001
Readmission	7	6	0.413
Reoperation	2	3	0.523
Treatment-related deaths	1	< 1	0.404
Hospital stay >2 days	94	52	<0.001
Postoperative adverse events % of patients (urinary tract infection, fever, pelvic cellulitis, abscess, venous thrombophlebitis, pulmonary embolus, bowel obstruction, ileus, pneumonia, wound infection, urinary fistula, bowel fistula, congestive heart failure, arrhythmia)	21	14	<0.001
Removal of pelvic and para-aortic nodes* % of patients	95.8	91.5	<0.0001
Median N° of pelvic nodes removed (IQR)	18 (12–24)	17 (12–23)	
Median N° of para-aortic nodes removed (IQR)	7 (4–11)	7 (4–11)	
Detection of advanced stage disease* % of patients	17	17	0.841
Conversion rate % (95% CI)		25.8** (23.7–28)	
Recurrence – Free Survival†			
3-year estimated cumulative incidence of recurrence§ %	10.24	11.39	
Estimated 5-year recurrence %	11.61	13.68	
Overall survival (estimated 5-year) %	89.8	89.8	
Quality of Life (QoL) scales within 6 weeks postsurgery† mean (SD)			
Functional Assessment of Cancer Therapy-General scores FACT-G•	89.6 (14.1)	85.4 (15.3)	0.006
Physical functioning*	66.5 (26.6)	55.9 (25.5)	<0.001
Pain interference with QoL**	8.9 (13.5)	12.7 (16.4)	0.021
Body image*	21.8 (4.4)	19.5 (4.7)	<0.001
Resumption of normal activities* (%)	67.3 (27.9)	56.6 (27.9)	<0.001
Fear of recurrence**	3.9 (3.6)	4.1 (3.9)	0.4
Additional treatment related symptoms** (fever, constipation, diarrhea, shortness of breath, ability to eat, problems urinating)	2.5 (2.5)	2.8 (2.7)	0.08

IQR – InterQuartile Range; CI – Confidence Interval; SD – Standard Deviation. * These results allowed us to conclude that the laparoscopic approach to staging was safe and did not compromise the ability to perform an adequate staging procedure.

** The conversion rate increased from 17.5% in patients with a body mass index (BMI) of 25 kg/m² to 57.1 % for patients with a BMI greater than 40 kg/m². † The estimated hazard ratio for laparoscopy relative to laparotomy was reported as 1.14 (95% CI 0.92–1.46).

§ The difference between recurrence at the 3-year mark was 1.14% (95% CI 1.278–3.996). † However at 6 months postsurgery, all reported differences in QoL scales between the two arms were not statistically significant, except for Body Image, which was 1.32 points higher (95% CI 0.61–2.04, p<0.001) in the laparoscopy compared with the laparotomy arm. • Higher scores indicate better quality of life. ** Higher scores indicate worse quality of life.

Table 2. Results of a recent meta-analysis of Randomized Controlled Trials (RCTs) quantitatively regarding clinical outcomes – complication rates and mortality rate – comparing laparoscopy with laparotomy for EEC.

Comparison items	No. of included RCTs*	RR (95% CI)	p value
Intra-operative complications	7	0.98 (0.62–1.55)	0.919
Post-operative complications	8	0.57 (0.40–0.83)	0.003
Total complications	9	0.59 (0.42–0.82)	0.002
Major complications**	8	0.53 (0.29–0.98)	0.042
Mortality	6	0.96 (0.66–1.40)	0.835

Adapted from [10]. * Nine RCTs with a total of 1263 patients were included into this meta-analysis [9,11–19]. ** Included: injuries of bowel, bladder, ureter, vessel, nerves; thrombo-embolic events such as deep venous thrombosis or pulmonary embolism; haematoma requiring surgical intervention; hemorrhage requiring transfusion and/or surgical intervention; wound dehiscence requiring surgical intervention or re-admission; wound infections including vaginal vault abscess, requiring surgical intervention and/or prolonged hospital stay and/or re-admission and/or treatment; other major complications [9,19].

cosmetic results. Laparo-endoscopic single-site surgery (LESS) and the so-called “mini-laparoscopy (ML)” and “micro-laparoscopy (mL)” have seemed to achieve these goals.

Lower post-operative pain and use of analgesics, and high patient satisfaction with cosmetic results were reported in EEC women subjected to a total LESS hysterectomy [21–23]. The nearly “scar-free” procedure and improved pain scores allowed by LESS surgery have a significant impact on body image, which has a cosmetic impact and helps patients cope with a past cancer diagnosis [24].

Furthermore, it was hypothesized that the LESS approach could possibly decrease morbidity related to visceral and vascular injury during trocar placement, post-operative wound infection, or hernia formation [24].

Randomized trials could be helpful to validate conclusions of preliminary retrospective studies [21–24] that showed that, in the hands of expert laparoscopic surgeons, LESS staging of EEC is safe and feasible, and results in similar surgical outcomes and lymph node retrieval rates as traditional laparoscopy and robotic surgery.

However, although single-port access has reduced invasiveness, it has increased the procedure’s complexity. Placing the endoscope and operating instruments through a single incision creates internal and external difficulties, both with the instruments and with the surgeon’s hands. Crossing the instruments to increase the range of motion requires a cross-handed technique, making surgical maneuvers more complex and less fluid. Moreover, this issue is reduced but not avoided, even using curved or articulated instruments and flexible scopes of different sizes and lengths. Therefore, LESS is not easy to perform. A major pitfall in this technique is also the learning curve required to develop surgical competence.

Early experience in this technique suggests that 15–20 cases are required for initial competence, with an additional 15–20 cases needed to master the procedure [23].

In a prospective study, instead, Holub et al. assessed the learning curve of standard laparoscopic surgery for the treatment of EC and reported that 25 laparoscopic staging cases may be required for a surgeon to achieve a flattening of the learning curve [25].

Thus, other authors tried to decrease invasiveness by preserving the classic tenet of laparoscopy – the triangulation. The technological improvement encouraged “rediscovering” miniaturized laparoscopic (ML) instruments 3 mm in size and 3.5-mm trocars. The term mL usually refers to endoscopes that are 2 mm in diameter. In ML and mL, trocar positions remain in the original setting of standard laparoscopy and the surgeon benefits from the experience already gained. This results in an easier adaptation, without establishing a completely new technique in opposition to LESS. However, the surgeon and all the surgical team should become confident with the procedure and learn necessary tricks, such as compensating the fulcrum effect and the tremor due to the small instruments. Placement of a ML or mL port results in only a skin needle puncture and its closure is secured by the application of a single steri-strip or derma-bond adhesive tissue, without need for any sutures. Some authors suggested that the delicate instruments, because of their extremely small diameter, have significant potential for causing inadvertent injury to the bowel and viscera [26]. However, others showed that the seriousness of the complications is directly dependent on the size of the perforation [27]. The cosmetic and pain control advantages are superior [28]. The use of ML and mL also has the potential to reduce the risk for trocar-site herniation and to decrease the incidence of wound complications, primarily by minimizing the consequences of wound infection. This is very important because surgical

Table 3. Robotic surgery compared with laparotomy and laparoscopy.

Study (year)	Surgical approach	No. of patients	Years age mean (range)	BMI median (range)	Mean operative time min (range)	LN count mean (range)	Rate of major complications	No. of conversion to laparotomy	Length of stay (range)	References
Veljovich et al. (2008)	Robotic	25	59.5 (36–85)	27.6 (18.7–49.5)	283 (171–443)	17.5 (2–32)	8	1	40.3 h (17–215)	[39]
	Laparotomy	131	63 (30–92)	32.2 (16.4–65.8)	139 (69–294)	13.1 (1–42)	20.6	NA	127 h (13–576)	
	Laparoscopy	4	54 (51–67)	24.6 (22–29)	255 (220–305)	20.3 (7–39)	NR	0	28.8 h (22–47)	
Bell et al. (2008)	Robotic	40	63±10.1	33±8.5	184±41.3	17±7.8	7.5	NR	2.3±1.3 days	[30]
	Laparotomy	40	72.3±12.5	31.8±7.7	108.6±41.4	14.9±4.8	27.5	NA	4±1.5 days	
	Laparoscopy	30	68.4±11.9	31.9±9.8	171.1±36.2	17.1±7.1	20	NR	2±1.2 days	
Boggess et al. (2008)	Robotic	103	61.9±10.6	32.9±7.6	191.2±36	32.9±26.2	2.9	4	1±0.2 days	[36]
	Laparotomy	138	64±12.8	34.7±9.2	146.5±48.8	14.9±13.7	21.7	NA	4.4±2 days	
	Laparoscopy	81	62±10.8	29±6.5	213.4±34.7	23.1±11.4	8.6	4	1.2±0.5 days	
Seamon et al. (2009)	Robotic	105	59±8.9	34.2±9	242±61	Pelvic 21±76; aortic 10±4,7	13	13	1 (1–46) nights	[35]
	Laparoscopy	76	57±11	28.7±6.9	287±55	Pelvic 22±8,4; aortic 11±5,3	14	20	2 (1–9) nights	

Adapted from [40]. NA – not applicable; NR – not reported.

site infection is a major contributor to postoperative morbidity, which increases the cost of care. Generally, EC risk factors include medical comorbidities that can inhibit wound healing, promote surgical site infections, and increase morbidity. In the study of Bakkum-Gamez et al., staging through minimally invasive surgery resulted in a 14-fold decrease in superficial incisional surgical site infections [29]. Therefore, in EC patient management, the choice of minimally invasive surgery procedures has consistently been shown to reduce this type of infection, as well as by reducing blood loss and transfusion risk, which have been linked to an increased risk of surgical site infections in gynecologic surgery [29,30].

A disadvantage of ML and mL is the quality of laparoscopic vision provided by the 3-mm and 2-mm scope, respectively, which is inferior in terms of image resolution, clarity, and light transmitting capacity in comparison to a 10-mm laparoscope. Other disadvantages are the suction-irrigation cannula, which, due to its small diameter, has poor flow characteristics and, in some cases, fails to maintain a clear surgical field, and the evacuation of smoke can also be compromised by the small-caliber ports, especially when an instrument is inserted [28].

Robotic surgery: Standard robotic surgery and single-port robotic surgery

Many authors concluded that it is not effective to perform laparoscopic hysterectomy in high-body mass index (BMI) women [31–34]. Bijen et al. noted that the risk of conversion from laparoscopy to laparotomy increases with BMI, with a rapid rise in women with a BMI >35 [31].

Robotic surgery appears to offer an advantage in the management of very obese women with EEC, with a lower conversion rate compared to standard laparoscopy [33,35,36]. In very obese patients, robotic surgery greatly facilitates the surgeon’s work through the availability of 3 instruments and more comfortable positioning, with a significant reduction of physical stress [24,37,38]. Retrospective cohort studies have examined the results of performing staging procedures for EC with robotic assistance compared to standard laparoscopy and laparotomy (Table 3) [30,35,36,39,40].

Assuming that intra- and post-operative complication rates and types of complications are similar between robotic surgery and

traditional laparoscopic surgery [36], it is generally accepted that minimally invasive surgery takes longer than an equivalent open procedure, therefore it is necessary to weigh the risks of prolonged anesthesia versus the benefits of a minimally invasive approach. In women with EC, surgical staging performed with the robotic approach requires shorter operating times than the same procedure performed with standard laparoscopy [35,36].

Studies have also documented that lymph node yield with robotic-assisted lymphadenectomy is similar to laparotomy [37,41]. Advantages of a robotic platform as compared to standard laparoscopy also include a faster learning curve. Seamon et al. published a detailed analysis of the learning curve for robotic hysterectomy and pelvic and para-aortic lymphadenectomy and reported that although each stage of the robotic procedure had a separate learning curve, overall proficiency was achieved after 20 cases [42].

An emerging area of minimally invasive surgical innovation is use of a single port utilizing the current robotic system. This has been accomplished with a multitude of creatively engineering single-site access ports through which the standard robotic arms are all placed. Escobar et al. first reported on the feasibility of gynecologic oncology applications with a newly designed robotic single-port in a cadaver series [43]. Fagotti et al. published one of the first experiences of robotic single-site hysterectomy in EEC patients, reporting that the real advantage of the robotic system compared to laparoscopic LESS is the annulment of the annoying conflict between the instruments, and the 3-dimensional view [44]. However, Fagotti et al. did not assess the versatility of the system regarding the lymphadenectomy. As this technology develops and is more widely assessable, it will need to be verified for the performance of hysterectomy as well as pelvic and para-aortic lymphadenectomy for the adequate treatment of EEC.

However, costs associated with the use of robotic assistance, which include cost of training and equipment maintenance in addition to the initial investment, remain very high. This cost may be negated over time by decrease in postoperative complications, hospital stays, and readmission, but this remains to be demonstrated.

Costs

Currently, in addition to improving EEC patient outcomes in the short- and long-term, cost effects of the various surgical approaches have become a research interest. In the study of Bell et al., total average costs of minimally invasive surgery for EC have been shown to be lower than laparotomy costs [30]. Bijen et al. published a review of cost for laparoscopic hysterectomy compared with abdominal hysterectomy, and they

introduced 2 terms: “direct medical cost” and “indirect cost”. Direct cost is defined as medical costs related directly to health care, including hospital stay, operative procedure, and treatment complications. Indirect costs relate to the impact on society, such as costs related to the patient’s absence from work or normal activities. In their analysis, the direct cost of laparoscopic hysterectomy was 6.1% higher than that in the abdominal hysterectomy group. The indirect cost of the laparoscopic hysterectomy was 50% of the cost for abdominal hysterectomy. With these definitions they found that the shorter hospital stay in the laparoscopic hysterectomy group compensated for the increased procedure cost [45]. Similar conclusions were reached by other authors, according to whom the most significant variables are the use of disposable instruments and the length of hospital stay [46,47].

Barnett et al. used a decision-making model to compare the costs associated with robotic, laparoscopic, and open surgery for the treatment of women with EC. Results demonstrated that laparoscopy is the least expensive surgical approach for the treatment of EC and that robotic approach is less costly than open surgery when the societal costs associated with recovery time are accounted for [48]. The results of Wright et al., comparing laparoscopy to robotic surgery for EC, showed substantially greater direct hospital costs associated with the robotic procedure [49]. In another study, Venkat et al. emphasized the differences in costs, charges, and reimbursements between laparoscopic and robotic surgery for EC. Venkat et al. concluded that, although robotic surgery increases direct costs and charges, the reimbursement to the hospital, surgeon, and anesthesiologist were not significantly different between the 2 surgical approaches [50]. Therefore, debate is ongoing regarding whether the minimally invasive surgical approach has the most benefit for the patient with EEC, the surgeon, and the healthcare system as a whole.

Surgical Technique with EEC (Stage I FIGO₂₀₀₉)

To date, the standard surgical technique for EEC consists of extrafascial total hysterectomy and bilateral salpingo-oophorectomy by laparotomy or minimally invasive surgery. The role of lymphadenectomy in the surgical management of women with EEC is an issue of current debate.

EEC can be subdivided into 3 risk categories of recurrence (Figure 1) [3].

Studies have shown that about 10–12% of positive lymph node metastases (LNM) are found in what is thought to be EEC. Even in the “low-risk” patients, up to 3–4% of LNM can be present. Currently, a systematic pelvic and para-aortic lymphadenectomy is the only way to accurately identify the presence of nodal disease in women with EC [2,51].

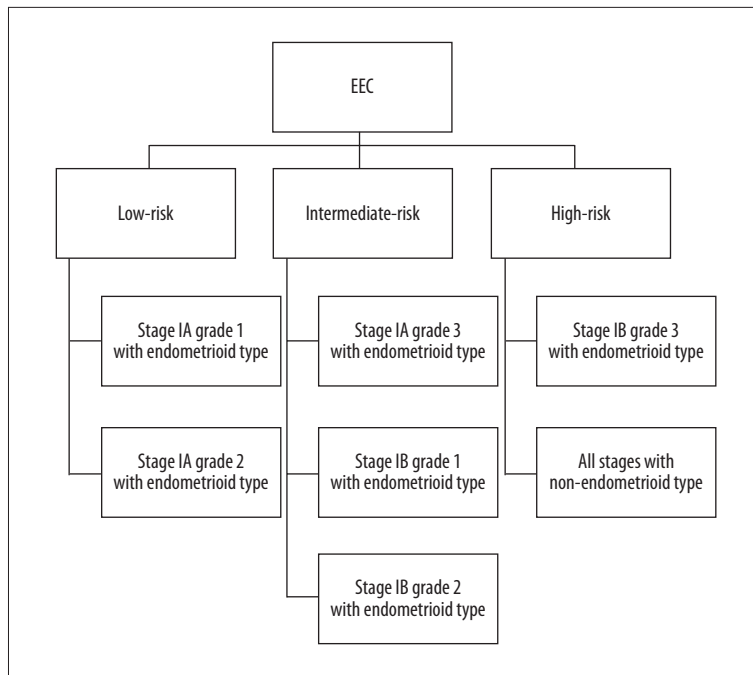


Figure 1. Risk categories of recurrence in EEC.

Two randomized trials comparing pelvic systematic lymphadenectomy to no lymphadenectomy in the surgical management of patients with supposed EEC demonstrated that lymphadenectomy improved surgical staging but not survival rates [52,53].

However, such studies have several limitations (Table 4). In the ASTEC trial, lymphadenectomy was selective rather than systematic (9 or fewer lymph nodes were removed in 35% of patients in the lymphadenectomy group). Neither the ASTEC trial nor the study of Benedetti Panici et al. included para-aortic lymphadenectomy. In these studies the omission of para-aortic lymphadenectomy would have negated the therapeutic effect of lymphadenectomy, because more than half of the patients with EC and pelvic LNM have para-aortic LNM, and about 10% of LNM occur exclusively in the para-aortic region [54,55], which is an important site of EC metastases as confirmed by sentinel lymph node investigation [56]. Removal of the para-aortic lymph nodes could explain the significant survival effect of para-aortic lymphadenectomy in EC shown by Todo et al. Similar to the ASTEC trial, findings from the SEPAL study have suggested that the survival effect of lymphadenectomy is restricted in low-risk patients, but in patients of intermediate- or high-risk a complete systematic lymphadenectomy in pelvic and para-aortic regions has substantial therapeutic effects [54].

Although it may not be therapeutic, lymphadenectomy is mandatory to avoid under-staging and the results of the lymphadenectomy should be used to guide the decision about appropriate adjuvant therapies and therefore to prevent unnecessary over-treatment or inappropriate under-treatment [57].

Currently, it is suggested to avoid a complete surgical staging for low-risk EEC but to perform comprehensive pelvic and para-aortic lymphadenectomy in patients with intermediate- and high-risk EEC [3,58].

The decision to perform systematic pelvic and para-aortic lymphadenectomy must take into account the general surgical risk of the patient and the risk for retroperitoneal LNM preoperatively and intraoperatively assessed [4].

Preoperative Evaluation of Lymph Node Status in Women with Supposed EEC

Understanding of several key factors – assessing histological subtype, grade, depth of myometrial invasion, and lymph node evaluation – is critical to making a conscious decision regarding the proper surgical procedure. In patients with supposed EEC, the incidence of LNM is low – about 1% for well-differentiated tumour limited to the endometrium up to 36% for poorly differentiated neoplasia in which invasion exceeds 50% of the myometrium [1]. LNM occur most frequently in the pelvic area and direct para-aortic drainage is estimated to arise in only 1% of EEC cases [59–61].

Women with negative nodes derive no benefit from unnecessary lymphadenectomy, and may develop short- and long-term morbidity related to this procedure [62]; therefore, preoperative staging of the local spread of disease is a critical step for tailoring the extent of surgery [63].

Table 4. Results and weaknesses of three large trials on the therapeutic role of lymphadenectomy (LND) in Early Endometrial Cancer.

Study [Reference]	Lymph-node removed		Overall survival* (univariate analysis)**		Follow-up	Weaknesses
	Median N° pelvic nodes	Median N° para-aortic nodes	HR (95% CI)	p value	Median months (IQR)	
MRC ASTEC trial [52]			1.16 (0.87–1.54)	00:31	37 (24–58)	1) Lymph-node dissection in the LND arm appears to be inadequate. 2) Para-aortic LND was not part of the study. 3) Patients who were found to have LNM at the time of surgery underwent secondary randomization, and therefore half did not receive adjuvant treatment. 4) 5% of no-LND arm had nodes removed with 27% of these patients demonstrating LNM, so the difference in outcome between the two arms is obscured. 5) Despite randomisation of a large number of women, the LND arm had 3% more poor histotypes, 3% more grade 3 lesions, 3% more lympho-vascular space positive cases, and 10% more with deep myometrial invasions, these differences suggest an higher risk of recurrence in the LND arm and may be substantial when overall survival is considered. 6) The follow-up period was short, with 35.7% of surviving patients followed-up for less than 3 years
LND arm	12 (range 1–59)					
No-LND arm	2 (range 1–27)					
Benedetti-Panici et al. study [53]			1.20 (0.67–2.13) [‡]	0.55 [‡]	49 (27–79)	1) Para-aortic LND was not part of the study. 2) Risk of recurrence was not considered in this study. 3) Adjuvant therapy was administered at the discretion of the treating physician after surgery, in patients at higher risk of recurrence on the basis of the histopathologic analysis of surgical specimen, this results in the lack of uniformity in the type of therapy used. 4) §7% of no-LND arm had 20 or more pelvic lymph-nodes removed, these patients were excluded from the per-protocol survival analysis; however, another 15% of no-LND arm had less than 20 pelvic lymph-node removed and these patients were no excluded from the per-protocol survival analysis
LND arm	26 (IQR 21–35)					
No-LND arm [§]	0 (IQR 0–0)					
SEPAL study [54]			0.53 (0.38–0.76)	0.0005		1) In the SEPAL study the risk was mainly classified according to the stage. Therefore, the significant survival effect of para-aortic LND, shown in this study, refers mainly to not EEC. 2) Adjuvant therapy was administered lacking of uniformity in the type of therapy used
Pelvic LND arm	34 (IQR 21–42)		0 (IQR 0–0)		94 (66–131)	
Pelvic and para-aortic LND arm	59 (IQR 46–73)		23 (IQR 16–30)		91 (60–129)	

IQR – InterQuartile Range; HR – Hazard Ratio; CI – Confidence Interval. * In ASTEC trial and Benedetti-Panici et al. study overall survival is for LND arm compared with no-LND arm. In SEPAL study overall survival is for pelvic and para-aortic LND compared with pelvic LND alone. ** A multivariable analysis of survival was conducted with different covariates from each of the three study, resulting in essentially identical conclusions. [‡] These values are per-protocol overall survival analysis, for intention-to-treat analysis are HR=1.20 (95% CI 0.70-2.07, p=0.50).

Role of imaging techniques

Depth of myometrial infiltration has been related to the likelihood of LNM, and both of these parameters may be assessed before surgery with imaging techniques.

Contrast-enhanced magnetic resonance imaging (MRI) has been shown to be superior to unenhanced MRI, ultrasonography, and computed tomography (CT) in the assessment of myometrial invasion (sensitivity 84–100%, specificity 71–100%) [64]. Diffusion-weighted MRI (DWI) has been shown to be very accurate in the assessment of deep myometrial invasion when combined with T2-weighted imaging, with a diagnostic performance similar to or slightly better than contrast-enhanced MRI [65].

A correlation between the degree of differentiation and the apparent diffusion coefficient (ADC) values has also been identified – high-grade adenocarcinomas typically have very high cellular density and lower ADC values than low-grade adenocarcinomas [66]. Therefore, it has been proposed that DWI should be included as an adjunct to conventional MRI in preoperative evaluation of EC. DWI may also be a viable alternative to contrast-enhanced MRI in patients not suitable to receive contrast material injection due to allergies. However, MRI is costly, time-consuming, and not always available [1]. Transvaginal ultrasound (TVS) is a simple, low-cost, noninvasive technique for myometrial assessment [1].

While some authors [67] report diagnostic accuracy of TVS as high as MRI in assessing the depth of myometrial invasion, others [1] showed that it is not reliable.

Computed tomography (CT) is not sensitive or specific enough to assess the depth of myometrial invasion, since there is relatively little contrast difference between tumor and myometrium [68].

CT scan and MRI are non-invasive imaging techniques extensively used to assess nodal spread of disease in patients with malignant tumors, including EC. Size of short-axis node diameter greater than 10 mm is the most accepted criterion for the diagnosis of suspicious nodal involvement. Unfortunately these morphologic imaging techniques have low sensitivity, ranging from about 20% to 65%, with specificity between 73% and 99% [69]. In the study of Lin et al., criteria combining lymph node size and relative ADC value increased the sensitivity from 25% to 83% for MRI in the detection of LNM in EC [70].

Positron emission tomography (PET) showed a low sensitivity in prediction of EC LNM and could not replace lymphadenectomy [69].

To overcome the lower spatial resolution of PET compared with MRI or CT, fused positron emission tomography/computed

tomography (PET/CT) was introduced. PET/CT combines the anatomic detail provided by CT with PET metabolic information. Park et al. compared the validity of PET/CT with that of MRI in the preoperative evaluation of lymph node status and reported that PET/CT had only slightly higher sensitivity than MRI in detecting LNM, suggesting that PET/CT cannot replace surgical staging of lymph node status. However, PET/CT had high specificity and negative predictive value (NPV) in detecting LNM, signifying it may allow the omission of lymphadenectomy in selected patients who are poor candidates for surgical staging; similar results were reported by Signorelli et al. [69,71].

Role of tumor markers

Tumor markers are not routinely used in clinical practice for EC, although some of them may be: CA125, HE4, CA19.9, CA15.3, CA72.4, M-CSF, CEA, and S-AA [72–77]. A sensitive serum marker may be of clinical value in supporting the preoperative staging process in order to individualize the treatment of women with supposed EEC. It is emphasized that, above all, HE4 and CA125 may serve as prognostic factors estimating the likelihood of extra-uterine disease and consequently assist the preoperative counseling of EEC patients.

CA125

Increased CA125 levels (>35 U/ml) have been reported in 11–33.9% of patients with EC [72] and have been correlated with stage, depth of myometrial invasion, histologic grade, lymphovascular space invasion, adnexal involvement, cervical invasion, peritoneal cytology, lymph node status, and clinical outcome [72,78–82]. Several studies investigated whether serum CA125 assay may provide additional information in the preoperative assessment of EC, especially in the detection of patients with high risk of microscopic extrauterine spread who need the lymphadenectomy, even if the appropriate cut-off level of CA125 for this is still uncertain [83]. Scambia et al. found CA125 levels >65 U/ml in 22% of patients without metastatic lymph node involvement compared to 58% of cases with histologically proven positive nodes ($p=0.022$) [84]. LNM have been significantly correlated with raised CA125 levels. Hsieh et al. showed that preoperative serum CA125 >40 U/ml has a sensitivity and specificity for screening LNM of 77.8% and 81.0%, respectively, suggesting that this marker may be considered a criterion for lymphadenectomy [80].

Although CA125 is routinely used in some practices, it has poor sensitivity and specificity [80,85]; hence, the critical importance of identifying a more reliable biomarker for patients with EC.

HE4

HE4 (Human Epididymis Protein 4) is a glycoprotein initially mentioned in ovarian cancer. Many authors have reported that HE4

Table 5. Role of preoperative serum levels of CA 125 and HE4 in Endometrial Cancer.

	CA 125	HE4	
Detection of Endometrial Cancer	Sensitivity	+/++	+++/++++
	Specificity	+++/++++	++++/++++
Detection of Early Endometrial Cancer	Sensitivity	+	+++/++++
Assessment of Myometrial Invasion (MI) for MI ≤50% or MI >50%	Sensitivity	+++/++++	++++/++++
	Specificity	++++/++++	++++/++++
Correlation with histologic grade	Present	Absent/low	
Correlation with LN status (Not all references found an association between HE4 and lymph-node status)	Sensitivity	++++	++++
	Specificity	++++/++++	+++
References	[72,78–85,87,90]	[86–92]	

+ If references report sensitivity and specificity between 0–20%; ++ if references report sensitivity and specificity between 21–40%; +++ if references report sensitivity and specificity between 41–60%; ++++ if references report sensitivity and specificity between 61–80%; +++++ if references report sensitivity and specificity between 81–100%.

is an accurate and sensitive serum marker for detection of EC (Table 5). Moore et al. found that HE4 is elevated in all stages of EC and is more sensitive in EEC compared to CA125 [86]. Angioli et al. found a sensitivity of 59.4% and a specificity of 100% (for 70 pmol/L cutoff); moreover, the marker was never increased in patients with benign disease, in contrast to CA125 [87].

Several studies suggest that HE4 may differentiate women with myometrial invasion less than 50% (stage IA) from those with myometrial invasion equal to or greater than 50% of the myometrium (stage IB) [87–90].

No such correlation between the HE4 levels and histologic grade was found [87,89,91]. However, in the study of Bignotti et al., an association between the HE4 levels and grade was observed when grade 1 tumors were compared with grade 2 or 2+3 [92].

Moreover, Angioli et al. found that the lymph node status directly correlates with the HE4 values and that median HE4 value in patients with stage I was significantly lower than in patients with stage III ($p < 0.001$) [87]. Bignotti et al. reported that high HE4 levels are associated with positive lymph nodes and presence of lymphovascular invasion [92]. Antonsen et al. also found significantly higher HE4 and CA125 levels in patients with LNM compared to those without, but in their cohort, CA125 was more precise than HE4 [90]. Conversely, neither Moore et al. nor Mutz-Dehbalaiie et al. found an association between HE4 and absence or presence of LNM [88,91].

Therefore, larger prospective clinical studies are needed to better assess the potential of HE4 as a new tool able to improve tailoring of surgical staging in women with supposed EEC.

Intraoperative Evaluation of Lymph Node Status in Women with Supposed EEC

Role of sentinel-node biopsy

In a systematic review, Selman et al. showed that sentinel-node (SLN) biopsy and MRI were the most accurate tests for predicting the lymph node status of women with primary EC, but these results must be interpreted with caution due to the variable quality of the studies available [93].

The SLN procedure has become a standard technique for the detection of nodal status and staging of the disease in patients with melanoma, vulvar cancer, and in breast cancer, but it is still at the feasibility-testing stage for EC [59].

The clinical value of SLN biopsy is based on its reliable NPV and high sensitivity in detecting EC LNM [60]. SLN is considered positive when it shows macrometastases, micrometastases, or sub-micrometastases [60,94]. A macrometastasis is defined as a single focus of metastatic disease per lymph node measuring more than 2 mm; a micrometastasis is defined as a single focus of metastatic disease per lymph node measuring between 0.2 and 2.0 mm; and a submicrometastasis is defined as a single focus of metastatic disease measuring less than 0.2 mm, including the presence of single, non-cohesive tumor cells [60,94].

Ballester et al. reported a high incidence of lymph node involvement, mainly micrometastases, by serial sectioning and immunohistochemical techniques on SLN, even in women with supposed EEC [94]. Ultrastaging of lymph nodes, using serial sectioning and immunohistochemistry, is a main focus of

the sentinel-node concept. This combined technique is time-consuming and expensive, thus its routine use is not extended to all nodes [60,94]. It has been reported that there is an increased risk of relapses in cervical, breast, and vulvar cancer in the presence of nodal micrometastases [95–97]. A case-control study in women with EC showed that removal of micrometastases was associated with a significant increase in disease-free survival [98]. However, controversy remains over the prognostic impact of micrometastases or isolated tumor cells and there is no consensus about the postoperative management of these patients – whether to perform further complete pelvic and para-aortic lymphadenectomy, external radiotherapy, or chemotherapy [99].

The greatest challenge in using the SLN technique in EC is to identify the injection site that properly represents the drainage of the tumor [59]. Hysteroscopy allows the injection of the tracer in the mucosal space just around the tumor, and, at least conceptually, should be the best way to delineate the drainage of the tumor. Moreover, hysteroscopic injection allows a complete detection of the drainage of the corpus uteri, directed both to pelvic and to para-aortic lymph nodes, thus decreasing the false negative rate [59]. The first report on hysteroscopy target-SNL technique, by Nikura et al., showed a detection rate of 82% with no false negatives [56]. Subsequently, Maccauro et al. and Raspagliesi et al. reported a detection rate of 100% with no false negatives [100,101].

Cervical injection for SLN detection in EC detects only a part, although conspicuous, of the lymphatic drainage of the uterus, but always shows unique pelvic drainage [59]. Although cervical injection can overlook some direct lymphatic drainage to the para-aortic area, its reproducibility and the prevalence of pelvic LNM in women with supposed EEC support its use [94]. The results of a prospective, multicenter study suggest that SLN biopsy using cervical dual labelling could be a trade-off between systematic lymphadenectomy and no dissection at all in patients with low-risk and intermediate-risk EEC, and that SLN biopsy alone could be enough to justify adjuvant therapy without the need for complete surgical staging in these patients [60].

Role of intraoperative frozen section

Intraoperative frozen section (FS) is a widely used approach to identify patients with supposed EEC who may need complete surgical staging [102]. The literature on this topic is controversial, with some suggesting FS to be reliable and others refuting this [103–105]. The reliability of FS is based on 2 critical factors: the rate of agreement between FS and paraffin section (PS), and the accuracy of the risk factors in predicting LNM [102].

Frumovitz et al. showed that FS analysis of tumor grade and depth of myometrial invasion is not always in agreement with

information provided by permanent sections [104]. A retrospective study comparing FS and PS reported 34.8% disagreement in assessing the grade of the tumor and 28% disagreement in assessing the depth of myometrial invasion, but the overall agreement on lymphovascular space invasion was 68.3%. According to this study, if only FS had been used for stratification risk, from 7% to 13% of patients would have received suboptimal treatment foregoing lymphadenectomy [102]. Quinlivan et al. also reported a 5–7% risk of suboptimal surgical treatment of EC patients when FS analysis is the basis of surgical management [103].

However, Kumar et al. recently studied a large prospective cohort of patients with EC, showing that FS provides highly reliable information on tumor size, histologic subtype, histologic grade, and depth of myometrial invasion [106]. Unlike the present study, no prior study used maximum tumor diameter in its risk stratification models for FS. This detail may represent a lost opportunity, because a smaller tumor diameter is associated with a lower-risk profile in EC [55]. In addition, maximum tumor diameter can be readily measured with minimal training, and the discordance rate of tumor diameter appears to be extremely low. Furthermore, in the study of Kumar et al., the use of multiple concrete variables (tumor size, histologic subtype, histologic grade, and depth of myometrial invasion) in the creation of a decision-making model to determine which patient's disease should be staged reduces the clinical impact of minor alterations in any single FS variable [106]. In their study, a clinically significant discordance between FS and PS occurred in only 1.3% of cases; therefore, Kumar et al. concluded that, despite skepticism about FS in the medical literature, FS can provide highly reliable data to guide intraoperative treatment decisions at institutions with appropriate pathology expertise [106].

Pristauz et al. found that FS on lymph nodes without SLN biopsy failed to detect nearly 2 out of 3 EC patients with positive nodes [107].

In a retrospective, multicenter study, the goal of Ballester et al. was to assess the diagnostic accuracy of intraoperative examination by FS and imprint cytology (IC) for the diagnosis of metastatic pelvic SLNs in EEC compared with the final histology [99]. Intraoperative assessment of SLNs has great relevance for immediate surgical management because, in the case of positive SLN, the surgical procedure can be completed by pelvic and para-aortic lymphadenectomy. However, the results of Ballester et al. indicate that overall sensitivity of intraoperative examination is moderate [99].

Proposal of a Management Algorithm

Based on the literature and our experience, we propose a management algorithm for EEC (Figure 2) that may be useful to

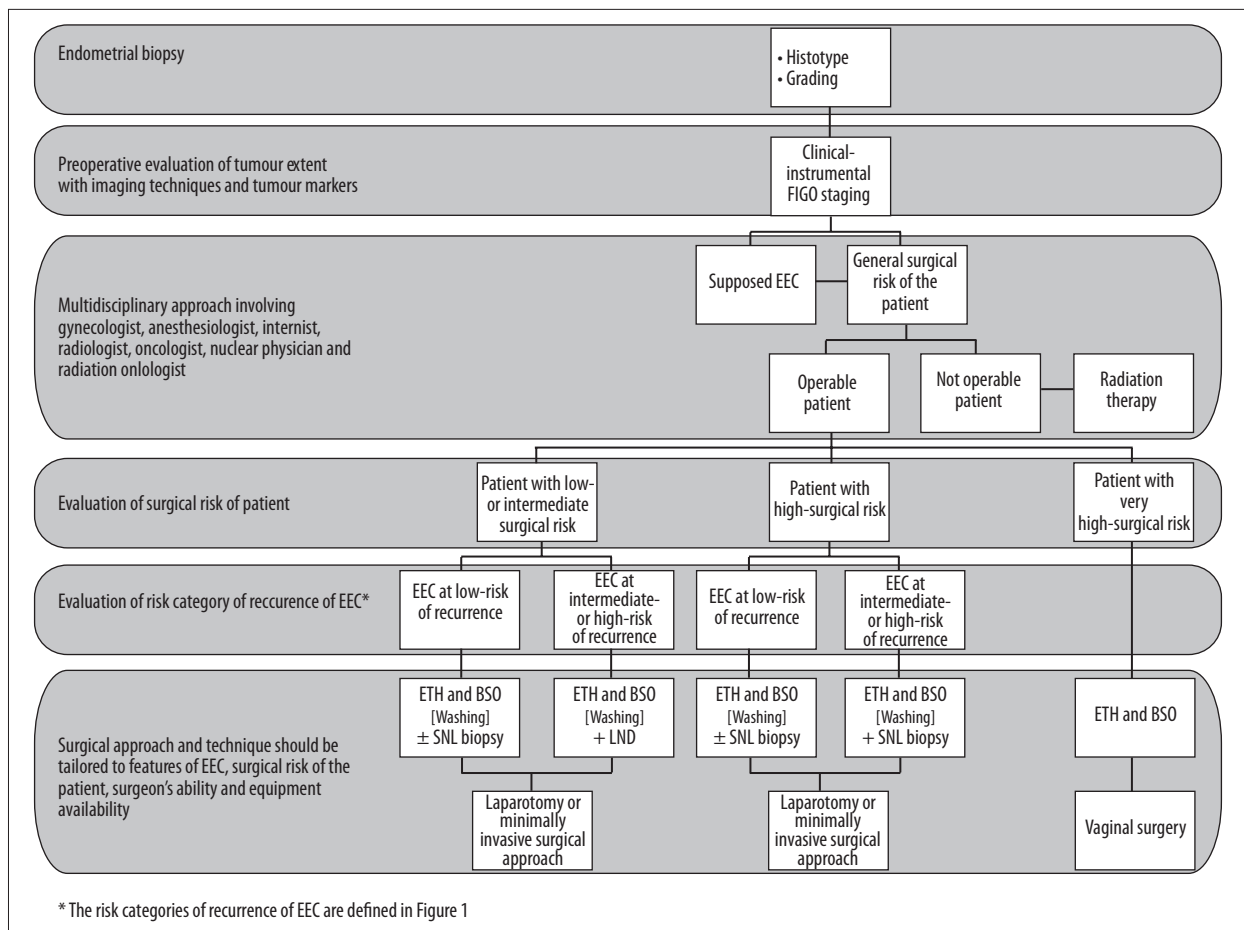


Figure 2. Early Endometrial Cancer (EEC): management algorithm. ETH – extrafascial total hysterectomy; BSO – bilateral salpingo-oophorectomy; SNL biopsy – sentinel-node biopsy; LND – lymphadenectomy.

disseminate a more standardized management strategy and is a tool that can be used in dealing with this group of patients.

The initial pretreatment evaluation, apart from history and clinical examination, should include endometrial biopsy that identifies women with EC, giving a general indication of the histologic subtype and grade, which are related to the likelihood of LNM. However, preoperative grading may underestimate tumor grades, since published data show that the concordance rate between biopsy and histologic examination is 63% [1].

Although clinical evaluation with diagnostic imaging and tumor markers have not yet proved to be accurate enough in the evaluation of tumor extent to replace surgical staging, it may enable an optimization of the surgical procedure and result in a better-tailored therapeutic strategy. Therefore, the radiologist is one of the first physicians who should be involved in the decision-making process.

In women with pretreatment staging of EEC, the general surgical risk (and, consequently, the most appropriate therapeutic

strategy) should be evaluated by a multidisciplinary team involving a gynecologist, anesthesiologist, internist, radiologist, oncologist, nuclear physician, and radiation oncologist.

Surgery is the standard of care for the treatment of EEC. However, women with EC are often aged and obese and have cardiovascular and metabolic comorbidities that increase the risk of peri-operative complications. In this context, internists and anesthesiologists have a prominent role in assessing whether the patient is medically fit for surgery. Approximately 3–10% of EEC women are deemed inoperable [108,109]. EEC patients considered unsuitable for surgery can be treated with radiotherapy alone as the primary modality of treatment. Radiotherapy techniques used have included various combinations of external beam radiotherapy (EBRT), high- or low-dose rate (HDR or LDR) uterine intracavitary brachytherapy, and HDR or LDR vaginal intracavitary brachytherapy [108,109]. Therefore, since radiotherapy alone becomes the only other curative alternative for medically inoperable EEC patients, the role of the radiation oncologist is very important in pretreatment counseling.

For EEC-operable patients, the choice of surgical approach (laparotomy or minimally invasive surgery) and technique (lymphadenectomy or no lymphadenectomy) should take into account the general surgical risk of the patient, the EEC risk of recurrence, the surgeon's ability, and the equipment availability.

In patients with supposed EEC, the incidence of LNM is low. As mentioned above, women with negative nodes derive no benefit from unnecessary lymphadenectomy, and may develop short- and long-term morbidity related to this procedure; therefore, preoperative and intraoperative evaluation of lymph node status could be a critical step for tailoring the extent of surgery.

Based on the literature and our experience, we suggest avoiding a complete surgical staging for low-risk EEC (also avoiding SNL biopsy) but to perform comprehensive pelvic and para-aortic lymphadenectomy in patients with intermediate-/high-risk EEC and low-/intermediate-surgical risk. Instead, we suggest that SLN biopsy alone could enable accurate surgical staging, avoiding invasive surgical procedures in patients with high surgical risk and intermediate-/high-risk EEC. Therefore, considering that SNL biopsy could replace lymphadenectomy in selected EEC patients and be sufficient to justify adjuvant therapy, the role of the nuclear physician is very important in pretreatment counseling and intraoperative management of EEC.

Furthermore, we suggest that, in patients with very high-surgical risk, vaginal surgery should be considered.

Finally, despite traditional use of adjuvant radiotherapy, when high-risk EEC features are found pathologically, patients may have compromised survival due to extrapelvic misdiagnosed disease, suggesting the need for effective systemic adjuvant therapy. Currently, there has been a fundamental paradigm shift to incorporate chemotherapy into the first-line management of high-risk EEC [110]. Therefore, the oncologist and the radiation oncologist have a prominent role in the first-line overall management of EEC patients.

Conclusions

In the management of patients with EEC, it is mandatory to avoid under-treatment and over-treatment, and it is necessary to appropriately assess the disease extent and to minimize complications that may result from invasive procedures and their adverse impact on quality of life.

The purpose of surgical staging is to determine the true extent of the disease and to tailor adjuvant therapy with the aim to reduce the relapse risk. To achieve this goal, it is necessary to better predict the depth of myometrial invasion and

the presence of lymph node metastases, while the other prognostic factors – tumor size, histologic subtype, and histologic grade – are more likely to be reliably estimated in the preoperative and intraoperative work-up.

The usefulness of MRI for the preoperative assessment of EC is increasingly being recognized. Newer MRI techniques, such as DWI, are currently being intensively investigated by researchers all over the world. This may provide valuable tools to improve preoperative diagnostic accuracy for a refined and tailored surgical procedure. An accurate biomarker or a panel of biomarkers such as HE4 and CA125 may be used as an additional tool in combination with imaging and clinical information when planning the treatment of patients with EEC. In this context, a better identification of the true extent of the tumor could replace surgical staging.

To date, advancements in minimally invasive surgical techniques allow extensive staging procedures to be performed with significantly reduced patient morbidity. Considering the ever-growing populations of the obese and the elderly, and the more recent data regarding obesity and the favorable outcomes with robotics compared with laparotomy and laparoscopy, it is not difficult to speculate that robotic surgery will become the first choice in EEC surgical management. However, important barriers still exist regarding the cost.

In women who are medically fit for surgery, advantages and disadvantages derivable from lymphadenectomy must be considered. So far, published research, including randomized studies, have failed to give definitive answers about the role of lymphadenectomy in the surgical management of women with EEC. In fact, mainly for ethical problems, it was not possible to carry out a randomized study that fully satisfies the requirements of the initial randomization. In most cases, the heterogeneity of enrollment, the personal decision of the surgeon, and the differences in surgical and postoperative management adapted to the individual case, have prevailed in the criteria for randomization, leading to an erroneous interpretation of the results.

The proposed algorithm is not intended to solve the problems discussed in this article, but could contribute to the standardization of the management of EEC. Its use on a large scale could improve the comparability of data and, perhaps, give more convincing answers to the several open questions.

However, when we have a demonstration of the feasibility of the SLN procedure with the confirmation of its potential benefits, SLN biopsy alone could enable accurate surgical staging, avoiding invasive surgical procedures, and could be enough to justify adjuvant therapy without the need for lymphadenectomy in selected EEC patients.

Therefore, optimal surgical management of EEC should provide a truly multidisciplinary approach, involving gynecologists, radiologists, nuclear physicians, anesthesiologists, oncologists,

and radiation oncologists. Progress in all these areas will allow safe and effective therapeutic solutions tailored to each situation in order to improve the quality of life of these patients.

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