Surgical management of endometrial cancer. A critical review

E. Halkia[1], N. Kalinoglou[1], J. Spiliotis[2]

[1]Department of Gynecology, [2]1st Department of Surgery, Metaxa Cancer Hospital, Piraeus, Greece

Summary

Endometrial cancer (EC) is a common gynecological malignancy. Prognosis depends on 3 main factors: histological subtype, depth of invasion into the myometrium and lymph node involvement.

Surgery remains the gold standard of treatment for this cancer. The aim of this article was to review the surgical approach and the new techniques along with the clarification of some controversial aspects concerning the management of advanced disease stages and the role of lymph node dissection.

Surgery of EC remains the treatment of choice in the management of early stage disease. The role of lymph node dissection remains controversial.

Key words: endometrial cancer, lymphadenectomy, robotic surgery

Introduction

EC is one of the most common gynecological malignancies with an annual incidence rate of 15-20 per 100,000 women in USA [1]. Lifetime probability of developing EC is 2.5% and dying from EC around 0.52%.

EC spreads towards the myometrial wall, cervix, and pelvic and paraaortic lymph nodes.

Prognosis depends on the histological subtype, depth of invasion into the myometrium, and lymph node involvement [1-5].

The new 2009 FIGO classification indicated new information about factors with prognostic significance. However, the extent of surgical staging, the definition of high-risk patients who benefit from complete staging, the number of lymph nodes, and the anatomical limits in the paraaortic area still lack standardization [2].

EC seems to arise through two different pathophysiological pathways: type I EC seems to be due to exposure to high concentrations of estrogens and type II seems to be independent of hormonal exposure. Type I is represented by endometrioid histology, whereas type II is composed of high-grade histologies with more aggressive behavior, i.e., serous or clear-cell carcinomas. Type I ECs are commonly diagnosed at an early stage and have a favorable prognosis, often with surgical treatment alone. Recurrent disease is usually local (pelvis being the most common site) and frequently curable with tumor-directed radiotherapy. On the other hand, type II ECs are more likely to present with metastatic disease at diagnosis and carry a poorer prognosis [6,7].

In addition to the traditional abdominal approach, vaginal, laparoscopic and robotic-assisted methods are currently also available for the surgical treatment of EC.

The aim of this article was to compare and evaluate these different treatment options in EC patients.

Fertility-sparing management

The occurrence of EC at a young age has been associated with prolonged unopposed estrogen exposure, for instance in women suffering from hormone-related disorders, obesity, infertility or polycystic ovarian syndrome (PCOS) [8].

EC in patients aged less than 45 years may have a more favorable prognosis than in older patients with more frequent well-differentiated tumors and limited myometrial invasion. Therefore, many attempts have been carried out to treat these women conservatively with fertility-sparing therapy using adjuvant progestins. However, conservative treatment entails the risk of progression [9].

Standard therapy for stage I EC is surgical treat-

ment including total hysterectomy, bilateral salpingo-oophorectomy, washings for peritoneal cytology with or without retroperitoneal lymph node dissection. A fertility-sparing therapy may be proposed in a well-selected group of women who strongly wish to preserve their fertility [8-10].

Young women with stage IA, grade I EC should undergo staging laparoscopy after informed counseling to exclude secondary ovarian neoplasia and lymph node metastasis before starting hormonal therapy. After finishing family planning, stage-adjusted operative (and radiation) therapy has to be initiated, frequently resulting in the discovery of higher tumor stages than initially diagnosed [11-14]. Ovarian preservation in the management of early-stage EC is still controversial.

Fertility-sparing treatment with oral progestins, especially medroxy progesterone (MPA) and megestrol acetate, represents the most commonly used hormone agents in this clinical setting.

Approximately 3/4 of women achieve a histologically documented complete response, but about 1/3 of them subsequently develop recurrence after a mean of 20 months.

Several successful pregnancies have occurred after a fertility-sparing treatment of EC, usually with assisted reproductive technologies (Table 1) [8].

Surgical management of stage I endometrial cancer

Surgical treatment for stage I EC includes intra-peritoneal cytology sample, total hysterectomy, bilateral adnexectomy and pelvic (at least 15 lymph nodes) and paraaortic (at least 10 lymph nodes) lymphadenectomy up to the renal vessels. In case of papillary-serous carcinoma or clear cell carcinoma it is mandatory to resect multiple peritoneal samples as well as to perform omentectomy because of the tendency of EC to spread to peritoneal surfaces. In clinical stage IA, grade 1 and 2 cases, lymphadenectomy is optional. More extensive parametrial resection (radical hysterectomy) does not improve the oncologic outcome in patients with stage I

Table 1. Selection criteria for fertility-sparing treatment in endometrial cancer

a) Grade I carcinoma
b) No myometrial infiltration in MRI or sonogram
c) No detection of suspicious pelvic or paraaortic lymph nodes
d) No evidence of adnexal tumors
e) No contraindication for hormonal treatment
f) Agreement for close follow-up (curettage every 3 months)
g) Stage-adjusted therapy after finishing desire for childbearing

EC [15]. The resected uterus should be examined intra-operatively, with or without frozen section, to assess the extent of the tumor.

Definitive histologic grade, myometrial invasion and lymph node involvement may differ substantially from intra-operative gross assessment and frozen section results [15-18].

Abdominal approach

Surgical abdominal approach for early-stage EC includes either a midline longitudinal incision from above the pubic symphysis to the xiphoid, or a wide Pfannenstiel incision as an alternative in patients with a lower body mass index. Intra-operative or post-operative complications of abdominal approach, like hemorrhage or bowel or ureteral injuries, occur at the same rate as in other abdominal gynecologic cancer surgery. Non-infectious wound breakdown occurs up to 10% in obese patients [19,20].

Laparotomy vs. laparoscopic surgical approach

In the last 15 years, the use of minimally invasive surgery is getting wide acceptance for the surgical treatment of patients with EC. Most studies examining laparoscopic vs. laparotomic surgery for stage I-IIa, grade 1-3 EC, have found no significant differences concerning staging completeness, lymph node metastasis, rate of perioperative complications and mortality [20,21]. Despite the controversies regarding EC staging by laparoscopy, its use in oncological practice is on the increase. It has been demonstrated that although laparoscopy usually requires a longer operative time and learning curve, it has the advantages of shorter hospital stay and better quality of life within the first 6 weeks [22]. Overall survival, disease-free survival, cancer specific survival, intra-operative complications and number of pelvic and paraaortic node yield were parameters proven equal for both techniques [23-26].

Vaginal hysterectomy and laparoscopically-assisted vaginal hysterectomy

Vaginal hysterectomy is a feasible alternative to abdominal approach. The only disadvantage of the exclusively vaginal approach is the impossibility of performing lymphadenectomy [27,28]. The ability to perform laparoscopic pelvic and paraaortic lymphadenectomy and laparoscopically assisted vaginal hysterectomy has shown some advantages presented in Table 2 [29-32].

The laparoscopic assistance adds to the vaginal

Table 2. Advantages of minimal invasive surgery in endometrial carcinomas

a) Less intraoperative blood loss
b) Less need for transfusion
c) Reduced duration of hospital stay
d) Faster recovery to normal daily activity
e) Less demands on postoperative analgesics
f) Approximately equal number of removed lymph nodes
g) Less surgical complications

surgical approach, and the combination is safe and feasible also in obese and elderly women, with shorter hospital stay and a faster return to full activity [33-36].

Robotic-assisted surgical approach

The role of robotics in the treatment and staging of EC continues to evolve but it has yet to be definitively determined. Advantages and disadvantages of robotic-assisted surgery are displayed in Table 3 [37-41].

The operative times in robotic-assisted and conventional laparoscopy are comparable, but longer than laparotomy. Perioperative complication rates of robotic-assisted surgery are lower compared with laparotomy. Also, no difference has been demonstrated in the conversion rates between laparoscopic and robotic-assisted procedures [42-47].

Shorter operative times, less blood loss and higher lymph node yield have been documented with robotic vs. conventional laparoscopy [48]. As with any new procedure, careful patient selection is essential during the initial learning phase in order to progress smoothly through the learning curve with low morbidity and excellent outcomes. This is particularly true for patients with EC, because they often have significant medical comorbidities that may compromise surgical outcomes [49].

Table 3. Advantages and disadvantages of robotic-assisted surgery

Advantages

a) Three dimensional vision system
b) Increased precision of instruments with more degrees of freedom
c) Tremor-free manipulation and advanced ergonomic positioning of the surgeon
d) Fast learning curve
e) Less intraoperative blood loss and rate of perioperative complications

Disadvantages

a) Absence of tactile feedback.
b) Large size of robotic equipment and larger skin incisions for inserting trocars

Surgery for stage II endometrial cancer

A retrospective review considering patients undergoing surgical treatment for EC has stratified them in a low-risk group (stage IA all grades and stage IB grade 1 and 2) and a medium to high-risk group (stage IB, grade 3 and stage IC-IV, all grades) [50].

In case of confirmed infiltration of the cervix uteri (stage II) from EC, increased survival rate has been demonstrated when performing radical hysterectomy. There is a significant difference in the 10-year survival in favor of radical vs. simple hysterectomy, while the benefit of adjuvant radiation therapy was either controversial or absent [51-53].

For aggressive histological subtypes –i.e. serous or clear-cell carcinoma– special attention should be paid to any evidence of extra-uterine disease. For these aggressive subtypes, the International Federation of Gynecology and Obstetrics (FIGO) staging system for EC mandates removal of the uterus, fallopian tubes and ovaries along with obtaining abdominopelvic washings for cytology and performance of bilateral pelvic and paraaortic lymphadenectomy. Because of the tendency of uterine papillary serous cancer to spread to peritoneal surfaces, as in the case with ovarian serous carcinoma, omentectomy and peritoneal biopsies have been advocated [54,55]. In selected stage II EC patients, experienced surgeons can do radical hysterectomy instead of simple hysterectomy and adjuvant radiotherapy, to reduce the complications of the combined treatment. The survival rates of these two treatment groups are not significantly different [56].

Surgical management of advanced endometrial cancer stages

Most recent studies have demonstrated a poorer prognosis for patients with advanced-stage EC. Maximum tumor debulking (possibly reducing tumors below 1 cm) is an acceptable practice in order to improve the effectiveness of adjuvant chemotherapy and/or radiation therapy and also to prolong overall survival [57-60].

In case of extra-uterine pelvic disease that involves either the vagina, parametrial tissues, bladder, or bowel / rectum, external radiotherapy with/without surgery, with brachytherapy, with/without chemotherapy have been proposed. If EC involves other intraabdominal organs (omentum, nodes, ovaries, peritoneal surfaces, ascites), total hysterectomy with bilateral salpingoophorectomy plus cytology, with/without maximal debulking and with/without pelvic and para-aortic lymph node dissection is the treatment of choice. In case of extra-abdominal / liver lesions, palliative treatments

are usually considered, such as total hysterectomy with bilateral salpingoophorectomy, with/without radiotherapy, with/without hormonal therapy and with/without chemotherapy [60].

Lymph node dissection

The role of lymph node dissection in EC is essential for the therapeutic management and overall patient survival.

Sentinel lymph node detection in endometrial cancer

Histological grade, the depth of myometrial involvement and lymph node status are the main prognostic factors in EC. Involvement of pelvic and paraaortic lymph nodes may guide the decision regarding the need for postoperative adjuvant therapy [61-63].

In EC, the sentinel lymph node procedure is increasingly used as an alternative to classical lymphadenectomy in order to avoid excess morbidity and improve the lymph node staging, while at the same time to preserve the control of regional disease. The concept of sentinel lymph node is based on the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph node basin, and the functioning of a first lymph node as an effective filter for cancer cells. These nodes / node are the sentinel lymph nodes and are predictive of the local nodal network integrity.

The identification of sentinel lymph nodes and their histological status can be used also to determine the extent of nodal dissection required [64-66]. Assessment of lymph node status in EC, especially in apparently early stages, remains an area of debate in the gynecologic oncology community. The purpose of lymphatic mapping is to identify one or more sentinel lymph nodes that would accurately reflect the status of the lymph node basins draining the uterus, in order to obviate the need for full lymphadenectomy without losing the information of the extent of cancer spread [67]. Two factors determine the applicability of lymphatic mapping in the daily clinical practice: the detection rate and the false negative rate. The false negative rate is the number of operations in which the sentinel lymph node is negative, but one -or more pelvic non-sentinel lymph nodes are positive, divided by the number of procedures in which any pelvic lymph node is positive. In other words, detecting lymph node metastasis in completion lymphadenectomy, when a sentinel lymph node was identified and found to be cancer-free. Obviously, this rate should be as close to zero as possible [68,69]. The detection rate is the proportion of cases where a sentinel lymph node is identified. Failed mapping is the opposite, and refers to cases in which no sentinel lymph node was identified. High detection rates can be achieved with a dedicated effort and increasing number of cases. Many different injection techniques exist, and surgeons should gain experience with whatever technique they chose until they can achieve high detection rates [70].

What about lymphadenectomy?

Regarding the previous comments, the FIGO surgical staging system for EC has not yet established any specifications regarding the type and extent of pelvic lymph node dissection. The extent (sampling or dissection) and performance of additional paraaortic sampling varies from surgeon to surgeon. Patients considered "low risk" for lymph node metastasis do not usually have a routine lymph node dissection. Moreover, comorbidities such as obesity or old age are also considered contraindications to a full pelvic and/or paraaortic lymphadenectomy [71].

Even though a small number of studies has not shown that lymphadenectomy has an impact on survival, most studies have demonstrated increased survival and have established lymphadenectomy as an important prognostic factor [72,73].

In a recent prospective study there was no benefit in terms of overall or recurrence-free survival from pelvic lymphadenectomy in women with early-stage EC [74].

In the literature the cut-off level for splitting patients undergoing lymphadenectomy into a limited sampling group and a multiple sampling group is around 10-12 lymph nodes. Although this number is essentially the median, it is basically a randomly selected range, and exceeding the cut-off level does not mean that a full dissection has been made. Moreover, the regions sampled also play a decisive role in the patient outcome. It has not yet been determined whether paraaortic lymph node dissection could play a substantial role in the routine treatment of all patients or only in cases of intermediate to high-risk EC [75,76].

A generally increased level of confusion exists regarding the performance of pelvic and paraaortic lymphadenectomy in patients with stage I and II endometrioid EC. Further research with prospective randomized studies is required in order to evaluate the significance of systematic paraaortic lymphadenectomy in relation to pelvic lymph node status as part of surgical treatment of EC, and to be able to indicate appropriate adjuvant therapy [77,78]. Pelvic lymph node yield over 12 is an independent prognostic factor for both overall and progression-free survival in patients with FIGO stage I and II with high risk pathology. Patients

with grade 3 EC, having more than 11 pelvic nodes removed, usually have improved overall and progression-free survival compared with patients with 11 or fewer nodes removed [79].

Conclusions

Surgical approach and accurate staging is the gold standard therapy in the primary management of patients with EC. Laparotomy as standard therapy could be replaced in many cases by laparoscopy or robotic surgery with many advantages, especially for better postoperative oncological outcome.

Intraoperative assessment of nodal involvement and myometrial invasion lacks the sensitivity and specificity as to select women who can avoid lymphadenectomy. Recently, sentinel lymph node detection and lymph node mapping studies present results which may shed some light regarding the lymph node dissection debate in EC.

So far, the greatest challenge in the surgical management of EC is standardization of pelvic and para-aortic lymphadenectomy strategies, in order to avoid unnecessary procedures and to offer complete staging with high survival rates.

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