

# A therapeutic algorithm for early-stage endometrial cancer: Indications, patient selection, and feasibility

E.M. Messalli, C. Scaffa, G. Mainini, M. Rotondi, A. Cafiero, L. Cobellis

*Department of Gynaecologic, Obstetric and Reproduction Sciences, Second University of Naples, Naples (Italy)*

## Summary

Endometrial cancer is the most widely spread gynaecologic neoplasm in industrial countries. Mode of spread includes direct extension, lymphatic and haematic diffusion. Lymphatic involvement, particularly, is a topic of wide debate due to the strong therapeutic implications associated with it. In this regard, anatomic-surgical staging is better in that it corresponds to real conditions whereas clinical-instrumental staging is still today incomplete.

*Key words:* Endometrial cancer; Therapeutic algorithm; Gynaecologic neoplasm.

## Introduction

A set of prognostic factors such as local status (T), histotype, grading (G), myometrial invasion (M), lympho-vascular involvement, peritoneal cytology, and lymphatic status have been singled out. These as a whole, together with the patient's general condition, surgeon's experience and availability of proper equipment, affect the therapy and outcome. Lymphadenectomy therapeutic choice particularly depends on lymph node metastatic risk. This is a function of M, G and T and it is greater for some histotypes, defined unfavourable, such as serous-papilliferous and clear cell. In this case lymph node aortic metastasis rises to 18% [7]. It is, instead, 40% in cases of positive pelvic lymph nodes, while it decreases to 2% in negative lymph nodes [7, 9]. On the basis of these data it appears that lymphatic metastasis goes on to subsequent sites. It can be concluded, consequently, that surgery in endometrial adenocarcinoma therapy is a basic premise. There are certainly several feasible therapeutic options based on accurate diagnoses in a suitable patient selection in order to reach a successful operability outcome near 100%.

## Indication - Patient selection feasibility

Endometrial cancer is the most widely spread gynaecologic neoplasm in industrial countries, showing rapid growth lately. Therapy has had an evolution in the progress of knowledge and oncological theory. This is conditioned by a number of factors such as the patient's general status, spreading mode and stage.

Several risk factors affecting the patient's general status justify a specific typology of women with endometrial cancer. These, generally, are women with a very high body mass index (BMI) and increased anaesthesiological risk.

Mode of spread includes direct extension, and lymphatic and haematic diffusion. Lymphatic involvement, particularly, is a topic of wide debate due to the strong therapeutic implications associated with it. There should be two main drainage pathways from the uterine corpus. One arises from the lymph nodes between the internal and external iliac arteries, and another at the aortic level reaching the origin of the ovarian peduncles. The two accessory pathways should flow from the round ligament which should empty into the inguinal lymph nodes and from lymphatic drainage directed to the group of common iliac lymph nodes [6, 7]. Several studies, however, have demonstrated that the main sites of lymphatic drainage are the obturator and the external iliac lymph nodes and that the spread happens step by step, first the pelvic and then paraaortic nodes [8, 9].

Therefore many doubts still persist on the utility of lymphadenectomy [10-13] as far as the interested lymphatic sites and the successive involvement of the same sites. Moreover there are not univocal opinions on the type of lymphadenectomy: selective, bioptic, therapeutic, and staging. In the last case how many lymph nodes are needed to be removed in order to obtain a valid oncological result?

Over the last ten-year period endometrial cancer staging has had an evolution as a consequence of the arising need for exploration of the whole abdominal cavity and the retroperitoneum.

Consequently anatomic-surgical staging better corresponds to real conditions than clinical-instrumental staging, which is still today incomplete.

A set of prognostic factors such as local status (T), histotype, grading (G), myometrial invasion (M), lympho-vascular involvement, peritoneal cytology, and lymphatic status have been singled out. These as a whole, together with the patient's general condition, surgeon's experience and availability of proper equipment affect therapy and outcome.

The prevalent therapy is surgical, but which type? There are manifold possibilities and the discussion is wide open especially regarding stage and vaginal,

abdominal, or laparoscopic surgery, with or without lymphadenectomy. The gold standard of reference is abdominal extrafascial hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytology and inspection of the retroperitoneum and the whole abdominal cavity with biopsy of suspected areas, pelvic and/or paraaortic lymphadenectomy [14] if indicated. Vaginal surgery, more widespread in some schools [12] before FIGO staging in 1988, must be considered at present. Such surgery is suggested in Stage I endometrial adenocarcinoma, only when other ways present greater risk, as in a patient with high anaesthesiological risk, severe obesity and advanced age [12-15]. Specific indications, though still debated, could be for a patient with low or very low metastatic lymph node risk for which a more extended operation should not have a propitious effect on survival, but, surely a negative impact on morbidity and future quality life [2, 16].

Contraindications to this approach are that uterine volume is higher at the 12<sup>th</sup> week of gestation and the possibility to remove it would require morcellation [15]; during the operation uterine rupture can occur and the uterine rupture serosa may be invaded. All these conditions could cause scattering of tumoral cells.

The benefits of this method must be ascribed to the quick execution, less surgical trauma and lack of laparotomy enabling a quicker return to mobility and recovery, less intra- and postoperative morbidity and for some, fewer vaginal relapses, all compared to a similar survival [12]. Disadvantages have to be identified: greater difficulty to execute salpingo-oophorectomy is seen in some [17] as a contraindication to the vaginal route, the impossibility to carry out abdominal and retroperitoneal exploration and/or peritoneal cytology, and therefore to execute a complete anatomic-surgical staging.

Laparotomic surgery is, as mentioned before, the gold standard. Advantages of laparotomy are identified in complete anatomic-surgical staging including evaluation of the abdominal and retroperitoneal cavity, lymphadenectomy and estimation and resolve of associated pathologies. The need for surgical staging should be taken from findings in 15% of cases [10, 18, 19] with worsening of clinical status after surgery.

Disadvantages, instead, come from more exacting operations, greater surgical and anaesthesiological risk, greater intra- and postoperative incidents, proportionate to exeresis, and slower physical recovery.

However, still today there are two topics of discussion about such surgery: the role of radical surgery and lymphadenectomy. From a CTF study [3] radical hysterectomy (Piver II-III type) was shown to be scarcely utilised as routine in endometrial cancer therapeutic management. Indeed in Western Europe [20] and North America [21], there are many centres not utilising it at all. Specific indications should be identified in Stage II adenocarcinoma surgical therapy, when there are particular histotypes (serous-papilliferous, clear cell), and grading G3, and myometrial M2 diffusion, and lympho vascular involvement in young patients in order to avoid adjuvant therapy and a similar outcome.

Radical surgery is associated with increased intra- and postoperative incidents and increased medical contraindications thus it is generally not recommended in Stage I disease. Incorrect diagnoses could expose patients to over-treatment and therefore the problem of a pretherapy diagnosis is addressed again [10].

The choice of therapeutic lymphadenectomy depends particularly on lymph node metastatic risk which is based on M, G and T and it is greater for some histotypes, defined as unfavourable, such as serous-papilliferous and clear cell. In this case lymph node aortic metastasis rises to 18% [7]. It is, instead, 40% in cases of positive pelvic lymph nodes, while it decreases to 2% when these lymph nodes are negative [7, 9]. On the basis of these data it seems that lymphatic metastasis goes on to subsequent sites. Knowledge of these scattering modalities and risk factors has made it possible to draw up a classification of lymphatic metastatic risk. Patients are at low risk if their classification is T1, M0/M1 and G1/G2 and thus it is possible to avoid lymphadenectomy [2]. Patients are at medium risk if they are classified as T1, M1/M2 and G3 and thus systematic pelvic lymphadenectomy with possible extemporary evaluation must be executed. Patients are at high risk if they are classified as T1/T2, with lymph node positivity and/or unfavourable histotypes for which systematic pelvic and paraaortic lymphadenectomy are suggested [13]. This outline has, however, a weak point - the postsurgical risk evaluation. Extemporary examination can resolve the problem, but even under the best conditions, it has a diagnostic accuracy of 90% [22]. Nor is there help from the macroscopic appearance of metastasized lymph nodes that become bigger in 10% of the cases only [10]. It thus appears that systematic and paraaortic lymphadenectomy are always indicated in high-risk cases [13], considering the prognostic importance of lymph node involvement and as this is the only way to obtain precise staging [23].

Laparoscopic hysterectomy was introduced in 1989 [24] and it was immediately extended to malignant pathologies including lymphadenectomy [25] but it was first Childers [26] who in 1992, used laparoscopic surgical therapy for endometrial cancer, followed by Kadar and Possover *et al.* [27, 28].

This surgery - laparoscopic-assisted vaginal hysterectomy (LAVH) with bilateral salpingo-oophorectomy and laparoscopic lymphadenectomy (LLA) - has the benefits of abdominal cavity and retroperitoneum exploration, uterus removal through the vaginal approach, safeness of salpingo-oophorectomy, and therefore a suitable anatomic-surgical staging, less blood loss, less hospitalization and quicker recovery [29, 30]. Instead, the disadvantages of this technique include greater operation time, impossibility of removing an uterus > 12 weeks of gestation without morcellation, greater difficulties in obese women, suitable instrumentation at a high cost, need of surgical skill and training [31, 32] in pelvic and oncological and laparoscopic surgery. This is, probably why, still today, there are few centres that execute such type of surgery. Contraindications, thus, include uterine serosa

propagation, uterine volume > 12 weeks of gestation, possibility of uterine rupture during surgical procedures, macroscopic involvement of the cervix, particular histotypes, extended visceral adhesions, cardio-pulmonic diseases and severe adiposity. On this last point there is not unanimous agreement because there are case reports stating the practicability and safeness even in women with variable degrees of adiposity [33].

According to Scribner *et al.* practicability of laparoscopic lymphadenectomy reaches 82% in patients with a BMI < 35 while it is only 44% in women with a BMI > 35 [34]. In spite of this such technique should be attempted in obese women due to fewer incidents and shorter hospitalization linked with the laparoscopic technique.

Laparoscopic surgery, thus, must be considered a practicable technique in endometrial adenocarcinoma because it is as oncologically effective as the abdominal technique [19, 25, 29, 30] and it allows removal of a comparable amount of lymph nodes [35, 36]. Survival, though with a limited follow-up, is also comparable.

Recurrences in correspondence to trocar portals which seem to be reduced when using low pressure and avoiding exsufflation through the same portals remains problematic [37]. Moreover the greater positivity of peritoneal cytology, in cases undergoing laparoscopic surgery, appears to be caused mainly by uterine manipulator use for cells passing through the tubes, so that the initial closing of these should reduce the problem [25].

Finally – the conversion degree from laparotomy to laparoscopic surgery is rather variable – from 0 to 36% [1, 4, 19, 25, 29, 30, 34, 38] and depends either on true incidents or clinical staging mistakes. These mistakes could be prevented so it is important to have a correct patient selection. Unfortunately, the possibility of clinical instrumental staging is still lacking. Presurgical staging does not correspond to surgical staging and is variable.

Patient selection therefore, should continue gradually. At the beginning, when a diagnosis of endometrial adenocarcinoma has been reached by determining the histotype and differentiation degree, clinical staging is defined by gynaecologic and hysteroscopic exams, CT and/or MRI scans. Then the patient is set from the anaesthesiological point of view with an evaluation of her general condition and the first conclusion for surgical capability is determined. Afterwards relapse risk is appraised and the best surgical mode can be identified. If all the above are carried out the selected surgery will have a better outcome for the clinical case under examination.

**Conclusion**

We can conclude, consequently, that surgery for endometrial adenocarcinoma is a basic point. There are certainly several feasible therapeutic options based on accurate diagnoses in a suitable patient selection in order to reach operability near 100%.

Certainly, laparoscopic oncological surgery on one side allows the feasibility of an operation by the vaginal route

(adhesiolysis and better control of the operation field in salpingo-oophorectomy) and on the other an oncologically correct surgery such as laparotomy. Today such a technique should be considered in endometrial carcinoma as suitable but not elective. Thus it should be applied in centres where oncological, surgical and laparoscopic techniques can be joined, and the practicability of such operation is codified by a suitable patient selection.

By virtue of what is stated above we propose a therapeutic algorithm for endometrial adenocarcinoma in early stages that summarises indications, patient selection and feasibility (Figure 1).

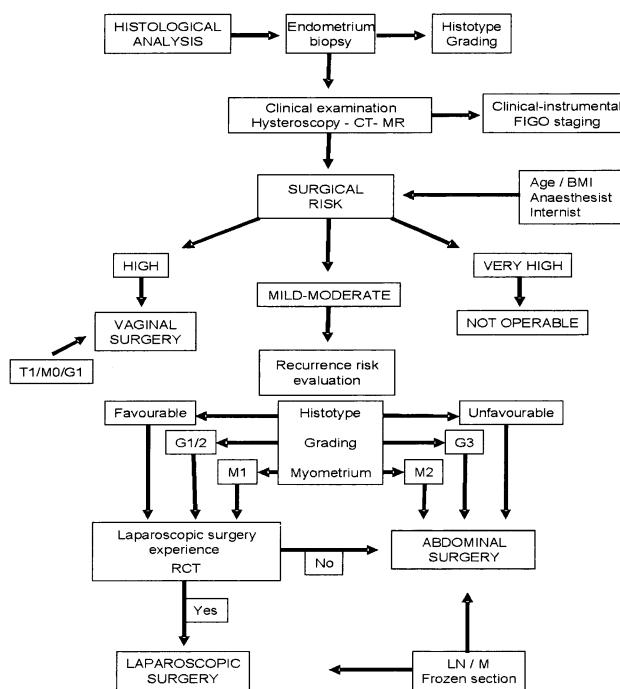


Figure 1. — Endometrial adenocarcinoma: therapeutic algorithm.

**References**

- [1] Eltabbakh G.H.: "Analysis of survival after laparoscopy in women with endometrial carcinoma". *Cancer*, 2002, 95, 1894.
- [2] Mariani A., Webb M.J., Keeney G.L., Haddock M.G., Calori G., Podratz K.C.: "Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary?". *Am. J. Obstet. Gynecol.*, 2000, 182, 1506.
- [3] Zola P., Jacomuzzi M.E., Mazzola S., Fuso L., Ferrero A., Landoni F., Gadducci A., Sartori E., Maggino T.: "Analysis of the evolution in the management of endometrial cancer in Italy: a CTF study". *Tumori*, 2002, 88, 481.
- [4] Fram K.M.: "Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in Stage I endometrial cancer". *Int. J. Gynecol. Cancer*, 2002, 12, 57.
- [5] Lissoni A., Landoni F., Leventis C., Pittelli M.R., Pellegrino A., Mangioni C.: "Carcinoma dell'endometrio: casistica dell'ospedale S. Gerardo di Monza". *Oncol. Ginec.*, 1990, 9, 181.
- [6] Benedetti Panici P., Cutillo G., Croce C., Maneschi F., Angioli R.: "Il significato della linfadenectomia nel carcinoma dell'endometrio". *APOG*, 2001, 5, 49.

- [7] Benedetti Panici P., Maneschi F., Cutillo G., D'Andrea G., Mancini N., Rabitti C. *et al.*: "Anatomical and pathological study of retroperitoneal nodes in endometrial cancer". *Int. J. Gynecol. Cancer*, 1998, 8, 322.
- [8] Mariani A., Webb M.J., Keeney G.L., Podratz K.C.: "Routes of lymphatic spread: A study of 112 consecutive patients with endometrial cancer". *Gynecol. Oncol.*, 2001, 81, 100.
- [9] Creasman W.T., Morrow C.P., Bundy B.M. *et al.*: "Surgical pathological study of endometrial cancer: a Gynecologic Oncology Group". *Cancer*, 1987, 60, 2035.
- [10] Creasman W.T., De Geest K., Di Saia J., Zaino R.: "Significance of true surgical pathologic staging: A Gynaecologic Oncology Group study". *Am. J. Obstet. Gynecol.*, 1999, 181, 31.
- [11] Holub Z., Kliment L., Lukac J., Voracek J.: "Laparoscopically-assisted intraoperative lymphatic mapping in endometrial cancer: preliminary results". *Eur. J. Gynaecol. Oncol.*, 2001, 22, 118.
- [12] Massi G., Savino L., Susini T.: "Vaginal hysterectomy versus abdominal hysterectomy for the treatment of stage I endometrial adenocarcinoma". *Am. J. Obstet. Gynecol.*, 1996, 174, 1320.
- [13] Yenen M.C., Dilek S., Dede M., Goktolga U., Devenci M.S., Aydogu T.: "Pelvic-paraortic lymphadenectomy in clinical Stage I endometrial adenocarcinoma: a multicenter study". *Eur. J. Gynecol. Oncol.*, 2003, 24, 327.
- [14] FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. *Int. J. Gynecol. Obstet.*, 2000, 70, 209.
- [15] Lellé R.J., Morley G.W., Peters W.A.: "The role of vaginal hysterectomy in the treatment of endometrial carcinoma". *Int. J. Gynecol. Cancer*, 1994, 4, 342.
- [16] Boronow R.C.: "Surgical staging of endometrial cancer: evolution, evaluation and responsible challenge. A personal perspective". *Gynecol. Oncol.*, 1997, 66, 179.
- [17] Marana R., Busacca M., Zupi E., Garcea N., Paparella P., Catalano G.F.: "Laparoscopically assisted vaginal hysterectomy versus total abdominal hysterectomy: A prospective, randomized, multicenter study". *Am. J. Obstet. Gynecol.*, 1999, 180, 270.
- [18] Eltabbakh G.H., Shamonki M.I., Moody J.M. *et al.*: "Laparoscopy as the primary modality for the treatment of women with endometrial cancer". *Cancer*, 2001, 15, 378.
- [19] Kuoppala T., Tomas E., Heinonen P.K.: "Clinical outcome and complications of laparoscopic surgery compared with traditional surgery in women with endometrial cancer". *Arch. Gynecol. Obstet.*, 2004, 270, 25.
- [20] Maggino T., Romagnolo C., Zola P., Sartori E., Landoni F., Gadducci A.: "An analysis of approaches to treatment of endometrial cancer in Western Europe: a CTF study". *Eur. J. Cancer*, 1995, 31, 1993.
- [21] Maggino T., Romagnolo C., Landoni F., Sartori E., Zola P., Gadducci A.: "An analysis of approaches to the management of endometrial cancer in North America: A CTF study". *Gynecol. Oncol.*, 1998, 68, 274.
- [22] Scribner D.R., Walker J.L., Johnson G.A., McMeekin S.D., Gold M.A., Mannel R.S.: "Surgical management of early-stage endometrial cancer in the elderly: Is laparoscopy feasible?". *Gynecol. Oncol.*, 2001, 83, 563.
- [23] Kilgore L.C., Partridge E.E., Alvarez R.D., Austin M., Shingleton H.M., Noojin F. III *et al.*: "Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling". *Gynecol. Oncol.*, 1995, 56, 29.
- [24] Reich H., Decaprio J., McGlynn F.: "Laparoscopic hysterectomy". *Gynecol. Surg.*, 1989, 5, 213.
- [25] Querleu D., Leblanc E.: "Laparoscopic surgery for gynaecological oncology". *Curr. Opin. Obstet. Gynecol.*, 2003, 15, 309.
- [26] Childers M.: "The virtues and pitfalls of minimally invasive surgery for gynaecologic malignancies: an update". *Curr. Opin. Obstet. Gynecol.*, 1999, 11, 51.
- [27] Kadar N.: "Preliminary prospective observations on the laparoscopic management of endometrial carcinoma using the two-stage approach to aortic lymphadenectomy". *J. Am. Assoc. Gynecol. Laparosc.*, 1997, 4, 443.
- [28] Possover M., Krause N., Plaul K., Kuhne-Heid R., Schneider A.: "Laparoscopic para-aortic and pelvic lymphadenectomy: experience with 150 patients and review of the literature". *Gynecol. Oncol.*, 1998, 71, 19.
- [29] Holub Z., Jabor A., Bartos P., Eian J., Urbanek S., Pivovarnikova R.: "Laparoscopic surgery for endometrial cancer: long-term results of a multicentric study". *Eur. J. Gynaecol. Oncol.*, 2002, 23, 305.
- [30] Lim B.K.: "The role of laparoscopic surgery in the management of endometrial cancer". *RCOG*, 2000, 107, 24.
- [31] Eltabbakh G.H.: "Effect of surgeon's experience on the surgical outcome of laparoscopic surgery for women with endometrial cancer". *Gynecol. Oncol.*, 2000, 78, 58.
- [32] Occeilli B., Narducci F., Lanvin D. *et al.*: "Learning curves for transperitoneal laparoscopic and extraperitoneal endoscopic paraaortic lymphadenectomy". *J. Am. Assoc. Gynecol. Laparosc.*, 2000, 7, 51.
- [33] Holub Z., Jabor A., Kliment L. *et al.*: "Laparoscopic hysterectomy in obese women: a clinical prospective study". *Eur. J. Obstet. Gynecol.*, 2001, 98, 77.
- [34] Scribner D.R., Walker J.L., Johnson G.A. *et al.*: "Laparoscopic pelvic and paraaortic lymph node dissection in the obese". *Gynecol. Oncol.*, 2002, 84, 426.
- [35] Gemignani M.L., Curtin J.P., Zelmanovich J., Patel D.A., Venkatraman E., Barakat R.R.: "Laparoscopic-assisted vaginal hysterectomy for endometrial cancer: Clinical outcomes and hospital charges". *Gynecol. Oncol.*, 1999, 73, 5.
- [36] Malur S., Possover M., Michels W., Schneider A.: "Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer. A prospective randomized trial". *Gynecol. Oncol.*, 2001, 80, 239.
- [37] Wang P.H., Yen M.S., Yuan C.C. *et al.*: "Port site metastasis after laparoscopic-assisted vaginal hysterectomy for endometrial cancer: possible mechanisms and prevention". *Gynecol. Oncol.*, 1997, 66, 151.
- [38] Magrina J.F., Mutone N.F., Weaver A.L., Magtibay P.M., Fowler R.S., Cornella J.L.: "Laparoscopic lymphadenectomy and vaginal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy for endometrial cancer: morbidity and survival". *Am. J. Obstet. Gynecol.*, 1999, 181, 376.

Address reprint requests to:  
M. ROTONDI, M.D.  
Via G. Mazzini, 5  
80059 Torre del Greco (NA) Italy