

Surgery for early stage endometrial carcinoma in the obese patient

ABSTRACT

Obese patients have increased risk of developing endometrial cancer proportional to the excess in body mass index. In this review, we explored the latest information on surgical management and its adaptation to the obese condition. Mini-invasive treatments (laparoscopic, robotic, vaginal, or combinations) should be systematically considered. Prevention and active treatment of obesity seem an interesting approach to reduce incidence and severity of the disease.

Key words: Body mass index; endometrial cancer; sentinel node

Introduction

Endometrial cancer (EC) is the fifth cause of feminine cancer in Europe, but the second gynecologic cancer worldwide. Thanks to an early patient's detection by postmenopausal vaginal bleeding, its prognosis is rather good with a global rate of 70% 5-year survival (which can rise to 95% in International Federation of Gynecology and Obstetrics [FIGO] stage 1 well-differentiated endometrioid tumors).^[1] However, this tumor usually occurs in aged patients, presenting comorbidities. This explains the important fact that 50% of EC patients die from a non-EC-related cause.^[2] In this review, we focused on the obese population and therapeutic options, especially for early stage disease.

Epidemiological Data

90–95% of endometrial tumors are of epithelial subtype, the others 5–10% consisting of sarcomas.^[3] It is clearly accepted that these carcinomas can be shared in two distinct histopronostic subtypes^[4] with specific epidemiologies. Type 1 carcinomas are of the endometrioid subtype. They are the most frequent and are of a good global prognosis. These tumors are linked to any situations of relative hyperestrogenism which stimulates endometrium development, unbalanced by an adequate progesterone secretion. Apart from rare iatrogenic

situations,^[5] hyperestrogenism is usually endogenic. It is observed in post- or peri-menopausal patients, often nulli- or pauci-parous, with a long life (early menses, late menopause) of ovulations.^[6] The polycystic ovarian syndrome^[7] is related to this condition of aborted ovulations. Obesity acts as a powerful cofactor of hyperestrogenism and consequently, is a strong factor favoring disease development and its related mortality.^[8]

Type 2 EC encompass all nonendometrioid carcinomas such as serous, clear cell, or undifferentiated carcinomas and carcinosarcomas. Of much poorer prognosis than type 1 tumors, they are not clearly related to a specific etiological condition, except for tamoxifen use which may favor the development of this tumor subtype.^[9]

In addition, 2–5% of EC are related to mismatch repair (MMR) system deficiency syndrome, as observed in the hereditary

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Lynch syndrome.^[10] It affects women at a younger age for the pathology, and MMR abnormality should be systematically sought in the tumor of these patients by immunohistochemistry since they are at a higher risk of other future malignancies (colon, kidney, bladder, or breast).^[11] Of interest is the fact that both type 1 (especially high grade) or 2 carcinomas have been reported in this context at a relative equal incidence.^[12]

Recently, genomic studies provide, besides the pathological classification, a new molecular classification of ECs with four specific prognostic signatures that may impact future personalized management of this disease.^[3]

Obesity is thus an important factor for the development of EC. The World Health Organization definition of obesity is clear and is based on body mass index measurements (BMI = weight [kg]/height [m²]). Obesity starts at a BMI ≥ 30 .^[13]

Obesity is observed worldwide with a great discrepancy according to socioeconomic level and activity of the population. Thus, obesity affects especially some islands, at first rank Nauru and Samoa islands, with 75% of population with mean BMI >30 , 34% in the USA and 20–25% for Europe and $<1\%$ in Vietnam, India or Japan.^[13] More worrying, is the general soaring of obesity, especially in some unexpected countries such as Australia (+81%), New Zealand +93%, even India (+33%)! Even in France, 20% of population is obese, with an increase by 42% in 30 years.^[14]

Apart from EC, obesity is responsible, through hormone imbalance and/or local inflammation, of other malignancies such as breast, ovary, colorectal, biliopancreatic, and even esophageal carcinomas!^[15] Specific biological mechanisms at the origin of EC development are complex and, for type 1 EC, involve both a relative hyperestrogenism status through conversion of circulating androgens into estrogens in adipocytes, not compensated by a progesterone secretion and a chronic inflammatory process through cytokines secretion.^[16] Other factors may favor the development of type 1 endometrial tumors such as type 2 diabetes mellitus or arterial hypertension, possible consequences of obesity as well. This explains why, although not exclusive, low-grade type 1 tumors are more frequently observed in the obese population than high-grade type 1 or 2 carcinomas,^[17] and at earlier stages. However, recent studies confirm that type 2 tumors are observed as well in an obese patient making their mechanism more complex than expected.^[18]

Hysterectomy in Obese Early Endometrial Cancer Patients

The current management of EC is based on surgery that enables tumor removal and staging.

As recommended by the most international guidelines, early stage EC needs, at least, a total hysterectomy, and bilateral salpingo-oophorectomy (TH-BSO). Pelvic and paraaortic node dissection are discussed in tumors with intermediate or high risk of recurrence and in type 2 tumors.

Even in higher stage, surgery should be the first option to exercise before any other treatment such as radiation therapy, chemo and/or hormone therapies, which are usually employed as adjuvant treatments or definitively in inoperable patients.^[19]

A total extrafascial hysterectomy without vaginal cuff is to be performed. Subtotal hysterectomy is never indicated in EC due to the not rare occult epithelial or stromal cervical involvement and may require implies secondary trachelectomy. The indication for radical hysterectomy is quite infrequent, even in case of overt cervical involvement since it does not impact survival.^[20]

Except in very young patients for whom fertility preservation management may be considered, BSO is systematically recommended. Indeed, EC patients are at peri- or post-menopausal age, the risk of occult ovarian metastasis is significant (6.7% for Fadare),^[21] as well as the risk of adnexal carcinomas.

The route to perform this operation, laparotomy, laparoscopy, vaginal approach, has been for long a matter of debate.

Thanks to the results of several randomized trials and meta-analysis,^[22] the situation is clearer. Laparoscopic surgery is clearly the method of choice to perform the surgical treatment and staging of early EC. Besides cosmetic advantages, the absence of laparotomy significantly reduces perioperative morbidity, length of hospital stay, and enables a quick recovery and return to previous activities.

To perform a TH-BSO, the issue of a full laparoscopic or a laparoscopically-assisted vaginal technique has been addressed in a small-size randomized study. Surgical outcomes were similar in both groups, but obese patients benefitted of a shorter operative time with the full laparoscopic approach.^[23]

Indeed, for obese and more for morbidly obese (BMI ≥ 40) patients, avoiding laparotomy, thanks to a mini-invasive

approach (laparoscopic or vaginal route), is always an advantage, as shown in a recent systematic review of the literature in obese EC patients (Blikkendaal *et al.* AGO 2015).^[24]

However, the adequate oncologic management of EC is not always feasible in obese or morbidly obese patients, because of the obesity itself and patient's comorbidities. In the largest LAP2 randomized trial that compared open to laparoscopic management of early EC, 26% of patients in the laparoscopy arm had to be converted into laparotomy because of obesity. Indeed, the requested pelvic and paraaortic lymphadenectomies could not be performed safely by all surgeons.

A good experience in laparoscopic surgery is required to manage obese patients. This experience is not restricted to the surgeon but concerns all the operative team. Nurses must be aware of a correct installation of the patient on the table. The anesthesiologists are especially concerned by these heavy patients often fragilized due to their comorbidities. Indeed, a prolonged high abdominal pressure due to both gas distension and Trendelenburg positioning may deeply affect ventilation and surgical tolerance. When all these conditions are fulfilled the rate of success of laparoscopic management is pretty high even in morbidly obese patients.^[25]

For surgeons, the main problem is the correct visualization of the operative field. The ports may sometimes be placed higher on the abdomen, above the umbilicus, especially for the optique. Then, a good pelvis exposure needs a sufficient and progressive Trendelenburg positioning, "negotiated" with the anesthesiologist.

A clear view of the pelvis may need additional bowel retraction thanks to transparietal suspensions, using sutures or disposable devices adapted to obese patients (T-lift® – Vectec France).

For dissections, the adequate use of integrated sealing-cutting instruments (Ligasure®-Covidien, Ultracision®-Ethicon, Thunderbeat®-Olympus...) will facilitate the operation and shorten its duration.

In case of a large uterus, the preventive coagulation/clipping of uterine arteries at their origin will reduce blood loss (Roman *et al.* JSLB 2008).^[26] In-the-field specimen morcellation is strictly forbidden to prevent tumor spread. Placement of uterine specimen in an adapted and strong endoscopic bag will enable the vaginal extraction and if necessary the in-a-bag hemisection of the enlarged specimen^[27] [Figure 1].

However, in some extreme situations (morbid obesity, history of laparotomies), laparoscopic surgery cannot be performed or tolerated. Except if obvious contraindication (abdominal spread, inadequacy between uterus size [on preoperative magnetic resonance imaging]^[28] and the vaginal access), an exclusive vaginal approach should be attempted, before convert into laparotomy, especially in elderly patients.^[29] As for laparoscopy, the use of integrated instruments makes this approach easier to complete. If BSO cannot be performed vaginally, the installation of a single port system will make this step easier to complete the operation laparoscopically through the vagina!

Lymph Node Dissections of Endometrial Cancer in Obese Patients

The most challenging problem in obese EC patients is the completion of the staging procedures.

Fortunately, the results of recent randomized trials and meta-analysis are helpful, since lymph node dissections do not improve survival rates but increase morbidity, especially in early stage low-grade EC^[30] (...which is the most frequent situations in obese or morbidly obese patients!). However, they remain indicated in case of higher stage or grade disease. Technically, when pelvis is adequately exposed, a latero iliac approach of the paravesical spaces is often easier to complete a pelvic node dissection, than the classical medial approach. In the future, it is likely that, in normal-appearing pelvic node basins, the sentinel node (SN) dissection may replace full pelvic lymphadenectomies, as shown in prospective nonrandomized studies. However, some technical aspects must be standardized, such as the technique of tracer injection and the best tracer to use. Deep and superficial intracervical injections at 3 and 9 O'clock in the cervix, although criticized since the method detects the uterus SN, rather than specific

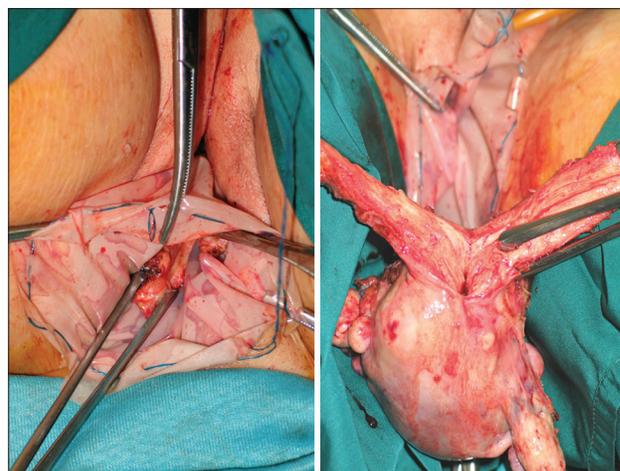


Figure 1: In-a-bag (Lapsac®-Cook medical) specimen hemisection

to tumor. This recurrent criticism is similar to the same issue concerning SN in breast cancer for which the intradermal injection of tracer provided same results as deep peritumoral injections.^[31] Furthermore, the hysteroscopic tracer injections are technically more complex to perform and are especially challenging in case of large intracavitary tumors. Thus, intracervical injections seem the easiest and most efficient method to use as a routine, with the highest detection rates even if paraaortic SN are less frequently observed.^[32] Some results of prospective studies of SN in EC show lower detection rates compared SN in cervix cancer.^[33,34] However, the regular use of the “algorithm” (site specific full dissection in the absence of SN detection) reduces the risk of false negative of the method to <5%, thus detection rates are equivalent to results in cervix cancer.^[35,36]

Concerning the tracers, recent studies assessing indocyanine green (ICG) and near-infrared (NIR) light detection report detection rates similar to radiotracer and superior to any kind of blue dye.^[37] The advantages of this technology are simplification of patient’s management (no need of preoperative injections of radiocolloid followed by scintigraphies) and prevention of useless irradiation. High BMIs do not impair detection rates, but bilateral detection rate seem higher when using combination of ICG and NIR light detection.^[38] However, the promising results of this policy deserve to be confirmed in larger prospective cohorts or a randomized studies.

When paraaortic dissection is requested in EC, it should be performed bilaterally, and up to the left renal vein.^[39] To complete this procedure laparoscopically is really challenging in obese EC and is with uterus size, FIGO stage, one of the major reasons for conversion into laparotomy with increased morbidity.^[40] Indeed, the transperitoneal approach is sometimes very challenging due to the thickness and shortness of mesentery. The extraperitoneal laparoscopic paraaortic approach as described by Dargent *et al.*^[41] may compensate, until some level, the difficulties of the transperitoneal approach and provides higher node counts even in higher BMIs, as highlighted in a recent comparative study of these two laparoscopic approaches (Pakish *et al.* GO 2014).^[42]

The Robotic Approach

The robotic approach has been claimed to facilitate the global management of obese patients whatever the indication, thanks to the mechanical elevation of the abdominal wall that enable to decrease abdominal gas pressure. In Seamon’s paper, it was shown that the rate of conversion to laparotomy was delayed for higher BMI when compared to laparoscopy (Seamon *et al.* GO 2009).^[43]

However, it must be stressed that a real experience in robotic surgery is mandatory to safely complete this operation in a reasonable operative time. Even in expert teams using the robot, the infrarenal paraaortic dissection is feasible in only 70% of obese compared to 88% in non-obese EC patients.^[44]

Finally, the choice of minimally-invasive techniques in morbidly obese patients result in longer operative times but lower rates of blood loss and shorter hospital stays compared to laparotomy, and should be preferred.^[45] Compared to laparoscopic approach, robotic surgeries provide comparable complication rates but charges are higher.^[46]

Nonsurgical Management of Early Stage

But even the best surgeons have know limits! In approximately, 10% of patients, extremely obese with an early stage EC along with life-threatening comorbidities (cardiovascular disease, organ failure due to diabetes mellitus, ventilation difficulties), general anesthesia is contraindicated or even mini-invasive surgery is not tolerated. In these situations, other alternative treatments must be considered. In a recent series of 43 high-operative risk patients with a FIGO I–III EC, the management consisted of definitive radiation therapy, encompassing external beam radiation therapy and high-dose rate intracavitary brachytherapy. 4.9% grade 3 toxicities were reported. With a median follow-up of 29 months, 8.3% local recurrences and 13% distal recurrences (restricted to grade 3 diseases) were observed with 2-year survival rate of 65%.^[47]

Prevention

Finally, although the adequate use of minimally invasive surgery has increased success rates of the surgical treatment of ECs in obese patients, the best policy is to prevent obesity by a well-balanced diet along with physical activity. It has been demonstrated that treatments of obesity strongly reduce the incidence of EC as well as several other malignancies^[48] and related cardiovascular mortality.^[49] early type 1 or atypical hyperplasia.

Recently, bariatric surgery has demonstrated its efficacy in reducing both the incidence of this disease by more than 70% as well as its recurrence risk!^[50] possibly thanks to the reduction of estrogen receptor expression.^[51]

Conclusions

Given its multiple advantages in terms of perioperative outcomes with no impairment of oncological results, minimally-invasive surgery (laparoscopy with or without

robotic assistance or vaginal surgery) should be definitively the favored approach in any early stage EC and should be considered in selected advanced stages, especially in obese patients.

Disease prevention by a large population education on the deleterious effects of junk food and positive effects of physical activity along with the active treatment of installed obesity, are the best means to reduce the incidence and improve the prognosis of this increasingly frequent disease.

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Conflicts of interest

There are no conflicts of interest.

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