

Review Article

Current Opinion in Gynecology and Obstetrics The Application of Different Surgical Methods in Endometrial Cancer

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Abstract

Endometrial cancer is a common gynecological malignancy in women, which accounts for the second in malignant tumor of female reproductive system. Obesity, high blood pressure and diabetes are risk factors for endometrial cancer. At present, the treatments of endometrial cancer focus on surgical treatment, followed by radiotherapy, chemotherapy and endocrine therapy. The progress of surgical method is transferring from traditional laparotomy, laparoscopy, single port laparoscope to Da Vinci robotic surgery system. Different surgical options should be personalized according to the patient's situation. We compared the pros and cons of different surgical methods and introduced the clinical value of the Sentinel lymph node mapping in hope of giving some information for clinic.

Keywords: Endometrial cancer, laparotomy, laparoscopy, robotic-assisted laparoscopy, single port laparoscopy, sentinel lymph node mapping

Introduction

Endometrial cancer (EC) is one of the common malignant tumors in women. It ranks the second in incidence rate among the malignant tumors of female reproductive system [1]. EC is more prevalent in developed countries. In 2021, it is estimated that there will be 66,570 new cases and 12,940 deaths, making uterine cancer the second most prevalent cancer among women in the United States, after breast cancer [2]. The prevalence rate of EC in elderly, obese, hypertensive and diabetic patients increased significantly. For those patients with EC who are in the early stage of EC, surgery is still a primary management. With the continuous development of medical technology, the surgical methods of EC have also been updated [3]. In this review, the different operative treatment for EC was compared in hope of providing useful information for clinicians.

Core tip

Endometrium cancer is one of the common malignant tumors in female genital system, surgical treatment is the main method to conquer it. With the progress of medical technique, the surgical treatment experiences from traditional laparotomy to laparoscopy to Da Vinci Robotic Surgery System. We summarize the pros and cons of the different surgical method and introduced the clinical value of the Sentinel lymph node mapping in hope of providing useful information for gynecologists.

Methods

Traditional open surgery

The procedure of traditional laparotomy includes retention of ascites or pelvic flushing fluid, comprehensive exploration of the pelvic cavity, hysterectomy and bilateral

salping-oophorectomy. The surgeon should check the surface of omentum, liver, peritoneum for possible metastasis and palpate suspected or enlarged lymph nodes in the aortic and pelvic areas. With the full exposure of operative field, the surgeon can directly touch the lesions and the operation is relatively easy. Even occurrence of intraoperative complications, the according management methods is relatively convenient and effective, so traditional laparotomy is the first choice for the treatment of EC. However, obesity is one of the high risk factors for EC; most patients are obese ($BMI \geq 30 \text{ kg/m}^2$) or even morbidly obese ($BMI \geq 40 \text{ kg/m}^2$). For patients with abdominal obesity, the operation is difficult, the interference of operation to the abdominal organs is large, so the hospital stay is long. What's more, the large incision of traditional laparotomy is more prone to experience fat liquefaction or incision infection. Subsequently, incisional hernia and slow postoperative recovery are easier to occur [4]. Doctors should carefully consider the indications of open surgery.

Minimally invasive surgery

In 1992, Childers and Surwit [5] first applied laparoscopic surgery to the surgical treatment of EC. After that, laparoscopic surgery has become more and more important in the treatment of EC. Laparoscopy has a magnifying effect and is more advantageous when cleaning lymph nodes, especially when cleaning lymph nodes in the obturator fossa. Laparoscopy facilitated to remove the obturator fossa lymph nodes and avoid damaging the blood vessels in the deeper parts of the obturator fossa.

Traditional laparoscopy vs Open surgery

Some scholars [6] have shown that compared with traditional open surgery, laparoscopic surgery can reduce intraoperative blood loss, shorten hospital stay, reduce postoperative complications, and improve the quality of life of patients.

Some researchers [4] confirmed that in the same number of lymph node resections, compared with open surgery, laparoscopic surgery has less pain, less body stress inflammatory response, and a greater decline in tumor markers. Though some scholars [7] suggested that morbid obesity is a relative contraindication to laparoscopic surgery, other researchers have confirmed that even in patients with obesity or overweight, compared with laparotomy, laparoscopy still has the advantages of less bleeding, lower complication rate and shorter hospital stay, which is consistent with the results of Uccella [8].

Chan [9] analyzed 1087 cases of morbidly obese patients

($BMI \geq 40 \text{ kg/m}^2$) and confirmed that compared with open surgery, robotic or traditional laparoscopic surgery has fewer complications and shorter hospital stay. Recently Galaal [10] conducted a meta-analysis and found that the OS ($HR=1.04$, $95\%CI=0.86-1.25$) and FDS ($HR=1.14$, $95\%CI=0.90-1.43$) were not significantly different between laparoscopic surgery and open surgery group. But some scholars found that laparoscopic surgery has the disadvantages of long operation time, which may lead to the formation of carbon dioxide accumulation. Hypercapnia can even produce severe acid-base balance disorders. Some scholars also believe that the rate of peripheral nerve damage and lymphedema of laparoscopic surgery is higher than that of open surgery, and it may also cause the spread of cancer cells and cancer metastasis [9].

In summary, laparoscopic surgery has the following advantage: less trauma and intraoperative bleeding, shorter hospital stay, fewer postoperative complications, faster recovery from operation and good quality of life. Laparoscopy is not less affected by the BMI of patient's, especially for morbidly obese patients. Although laparoscopy has above mentioned advantages, it still has the following limitations: (1) The operation time is longer, leading to hypercapnia and even serious acid-base balance disorders, which may be related to the patient's condition and the proficiency of the surgeon; (2) It has the risk of cancer cell spreading, leading to recurrence of cancer; (3) For morbidly obese patients, there are requirements for equipment for the specifications of Troca.

Da Vinci robotic surgery system

The Da Vinci robotic Surgery System is established on the basis of traditional laparoscopic surgery and is currently used in various gynecological operations such as total hysterectomy and pelvic lymph node dissection. Since the Da Vinci robotic surgery system was approved by the US Food and Drug Administration (FDA) for gynecologic surgery in 2005, it has gained wide attention as a new minimally invasive surgical system.

Da Vinci robotic surgery system vs. traditional laparoscopy

In traditional laparoscopic surgery, the surgeon operated in a relatively small abdominal cavity with the limited field of vision and space, which restricted the movement range of the laparoscopic instruments, leading to the failure of fine separation, suture and some special lymph node dissection.

The Da Vinci Robotic Surgery System has a robotic arm with high flexibility and mobility, which can eliminate the

limitation of human hand shaking and reduce operating errors. With the three-dimensional imaging and a more clearer surgical field of view, it improves the precision of procedure and avoids damage [10]. Some scholars confirmed [11,12-14] that compared with traditional laparoscopy, The Da Vinci robotic surgical system has less intraoperative bleeding, more total lymphatics, short hospital stay, light postoperative pain, quick recovery, and less intraoperative complications. Some scholars believe that [15] traditional laparoscopic and robotic surgery have similar operative time, both of which are longer than open surgery, which may be result from unfamiliarity with the machine and the limited speed of instrument assembly. Lim [16] found that to get experienced surgery skill, 24 cases are needed for robotic surgery, while 49 cases are need for traditional laparoscopic. It is easier for surgeon to achieve proficiency in robotic surgery. With fast assembly of the instrument and increased proficiency in operation, the time of robotic surgery is expected to decrease.

Although the Da Vinci Robotic Surgery System has many advantages as above, the maintenance of the machine requires huge costs, which increase the economic burden of patients. The corresponding indications and contraindications to the system are still not standardized. The size of machine is large, which demands enough space. Meanwhile, the surgeon lacks tactile feedback, it is difficult to perceive tension during clamping and coagulation, which leads to poor hemostasis and loose knots [17]. The Da Vinci robotic surgery system needs to be developed in technology and equipment, but it has a huge advantage over traditional laparoscopy and is an important surgical method for the treatment of EC.

Single-channel laparoscopic technique

With the continuous development and progress of medical technology and the increasing demand for minimally invasive wounds, the single-channel laparoscopic technology gradually appeared. With a channel of 15~30mm in diameter established in the umbilicus, a multi-channel cannula was put into the abdominal cavity for operation.

We enter the abdominal cavity through the physiological orifice of the human body, the number of puncture role is less and the wound is more beautiful, which significantly decrease the occurrence of complication caused by puncture. Foreign scholars have reported that [12] the use of analgesics and the pain scores after operation was significantly decreased in patients treated with single-channel laparoscopy than those treated with traditional laparoscopy, meanwhile there is no statistical difference in

postoperative complications, length of stay and treatment expense between the two groups. However, single-port laparoscopic technology has shortcoming such as blind field of vision, crowded equipment and lack of surgical triangle, and the surgeon may experience in coordination and interference in the exchange of left and right hands, which limits its development. Moukarzel [14,15] conducted studies on EC patients, and the results showed the surgery time and intraoperative bleeding was not statistically significant between robotic single port laparoscopy and traditional robotic laparoscopy. The treatment effects of the two groups were equivalent, but the single port group had a shorter hospital stay. Corrado [18] prospectively collected data of 125 cases of EC patients undergoing robotic single port laparoscopic hysterectomy. The total operation time was 122 minutes (35-282), and the average blood loss was 50 ml (10-250). 21 patients underwent pelvic lymph node dissection (16.8%), the median number of pelvic lymph nodes was 13 (3-32), and the average discharge time was 2 days (1-3). No intraoperative complications occurred.

Although robotic single port laparoscopy has many advantages, it still has following limitations: (1) The cost of equipment is expensive, which increases the economic pressure on patients; (2) There are fewer types of supporting equipment, and there are limitations in equipment selection; (3) The technical requirements for the surgeon are very high, especially for gynecological malignant tumor surgery. The report on single-channel laparoscopic technology research is seldom, the surgical indications and contraindications are still not standardized, and there are many problems to be resolved. Even with the shortcoming mentioned above, single-channel laparoscopic technology especially robotic single-port laparoscopic technology is expected to play a greater role in minimally invasive surgery.

Full staging surgery

As we mentioned above, the majority of patients with EC are in stage I of the FIGO staging, which provides an opportunity for surgical treatment. Lymph node metastases are an important mode of metastasis in endometrial cancer and survival rate is significantly lower in EC patients with pelvic or para-aortic lymph node metastases [19]. Evidence shows that 20% of early stage patients have occult metastases in the final pathological findings, which can be effectively prevented by lymphadenectomy [20]. Besides, the status of the lymph nodes and the presence of distant metastases are the most important factors in determining patient prognosis and the choice of adjuvant treatment modality. Therefore, the decision to perform lymphadenectomy during surgery has always been a hot

topic of discussion.

Systemic lymphadenectomy

It was previously suggested that systemic lymphadenectomy was associated with improved survival in patients with EC [21-23]. Kitchener conducted a large randomized controlled study concluding that systematic pelvic lymphadenectomy did not improve OS and DFS in early stage EC patients and concluded that lymphadenectomy should not be used as a routine procedure in staging surgery, which is consistent with the study by Benedetti [24,25]. Some studies [26] have found that systemic lymphadenectomy brings a series of complications, such as vascular nerve injury, lymphedema, and lymphoid cysts. Thus, there is an urgent need for a better, less harmful and more accurate way to assess the status of patients' lymph nodes.

Currently, the most commonly used criteria are the "Mayo criteria" proposed by Mariani et al. This means that lymph node dissection can be omitted in patients in the low-risk group (meeting all of the following criteria): (1) endometrioid type, grade G1 or G2; (2) myometrial invasion < 1/2; (3) tumor diameter < 2 cm). According to the Lirong Zhai [27], this criterion possesses 90% sensitivity but only 36% specificity, with nearly 80% of patients without metastases undergoing lymph node dissection. Furthermore, the criterion is dependent on intraoperative frozen sections (FS) and pathologists, with approximately 18% of EC patients staged up in the final pathology report.

Sentinel lymph node mapping

The sentinel lymph node (SLN) is the first lymph node through which a lymphatic metastasis from a primary malignancy passes through the regional lymphatic drainage pathway, and can indicate lymph node involvement throughout the drainage area. In 1996, Burke and his teammates first reported the SLN biopsy for EC [28]. In recent years, sentinel lymph node mapping for EC has been considered a new technique to avoid systemic lymphadenectomy and thus reduce the side effects associated with the surgery.

Marcos Ballester [29] conducted a multicenter trial to evaluate the accuracy of sentinel lymph node biopsy in 125 patients with early EC and their results showed an overall detection rate of 89% and a negative predictive value of 97%. Rossi [30] also conducted a multicenter, prospective study of 340 patients with early EC, which resulted in a sensitivity of 97.2% and a negative predictive value of 99.6%. Persson [31] found a sensitivity of 100% and a negative predictive

value of 100% for sentinel lymph node biopsy in patients with high-risk type of early EC. More recently, a study by Cusimano [32] also found a sensitivity of 96% for sentinel lymph node biopsy, a negative predictive value of 99%, and a false negative rate of 4% in patients with intermediate to high-grade EC. In agreement with a Meta-analysis by Beatrice Cormier that included 4915 cases [33], SLN testing is a feasible, valid and accurate method to predict lymph node metastasis in EC.

One of the risk factors for recurrence of endometrial cancer includes the presence of tumor micrometastases and isolated tumor cells. Lymphadenectomy usually requires removal of a large number of lymph nodes, makes it challenging to perform serial sections of approximately 5 um thickness on the entire specimen, and makes it difficult to diagnose microscopic lesions with conventional HE staining. Ultrastaging involves the use of enhanced pathologic techniques, including deeper serial sections and immunohistochemical (IHC) staining, to increase the detection of malignant cells in SLN. Niikura [34] obtained 74 SLNs in 20 EC patients, with a detection rate of 5% for micrometastases. In contrast, the detection rate among 1350 non-SLN was only 0.3%. It suggests that SLN is a promising and feasible means of detection for micrometastatic lesions. SLN combined with suprapathologic staging techniques will help in the diagnosis of micrometastatic lesions.

However, morbid obesity (BMI > 40 kg /m²), pelvic organ adhesions, tortuous vascular course of the patient, endometrial damage and disrupted lymphatic drainage (tumor invasion, endometrial inflammation, myofiltrative infiltration, etc.) or tracer selection may affect SLN detection rates and increase the possibility of false negatives [35,36]. This will be ameliorated by operator experience, combined use of tracers, and multiple site injections. As an alternative to systemic lymphadenectomy, SLN mapping has great clinical application, providing accurate information about lymph nodes status while reducing complications. However, the application of SLN mapping has not yet clarified its significance for the long-term prognosis of EC patients, and a series of further clinical studies with large samples are still needed.

Summary

Endometrial cancer is one of the common gynecological malignancies, and its incidence is increasing year by year. With the continuous development of medical technology, patients have higher and higher requirements for medical treatment techniques. From traditional open surgery, laparoscopic surgery, single port laparoscopic surgery to

today's Da Vinci robotic surgery system, surgical methods for gynecological malignant tumors experiences rapid development, all of which provides a variety of surgical methods for the treatment of EC. Tumor treatment is also gradually moving towards the era of precision therapy, which requires the operator to implement an individualized treatment plan for the patient's condition. Sentinel lymph node detection, as an alternative to systemic lymph node dissection, provides an additional method for clinicians to perform staging procedures. For those obese patients, minimally invasive surgery may be a better choice. In short, minimally invasive surgery and SLN mapping has a broad application prospect in the treatment of EC.

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