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REVIEW

Minimally invasive surgery for endometrial cancer: a comprehensive review

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Abstract
Purpose of review The objective of this article is to review the recently published literature on the use of minimally invasive surgical approaches for patients with endometrial cancer.
Methods Narrative review of the pertinent literature on traditional laparoscopy and robotically assisted laparoscopy for the treatment of endometrial cancer.
Results Multiple studies have shown that minimally invasive surgical approaches for the treatment of endometrial cancer reduce blood loss, length of hospital stay and the incidence and severity of post-operative surgical complications compared with laparotomy. Minimally invasive techniques maintain equivalent oncologic results with regard to the number of dissected lymph nodes and overall and disease-free survival rates. Robotically assisted laparoscopy compared to traditional laparoscopy reduced the conversion rate to laparotomy, further reduces intra-operative blood lose and has significant ergonomic advantages for the surgeon. Laparoscopic and robotic surgery techniques are particularly advantageous in obese patients, reducing peri-operative and post-operative abdominal wound complications.
Conclusions A thorough review of the literature indicates that minimally invasive approach has a number of established advantages over laparotomy that makes it the surgical treatment option of choice in endometrial carcinoma patients.

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Introduction

Surgery is the cornerstone of managing patients with endometrial carcinoma. Traditionally, staging includes exploratory laparotomy through a midline vertical skin incision, peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, with or without pelvic and para-aortic lymphadenectomy and depending on histology, omentectomy [1, 2].

Post-operative treatment recommendations include radiation and/or chemotherapy tailored according to the stage of disease, histologic cell type, grade and lymph node involvement [3]. Accurate surgical staging is the first step toward making adjuvant treatment recommendations. Providing customized adjuvant therapy in patients with advanced disease while minimizing unnecessary treatments in early stage endometrial cancer patients can eliminate unwarranted complications and reduce costs. Uterine carcinoma patients are generally elderly and obese, with significant co-morbidities such as cardiovascular disease, hypertension and diabetes. Therefore, it is essential, particularly in this population, to decrease intra-operative and post-operative complications.

Methods

Computerized literature search of electronic databases (PubMed, EMBASE, Cochrane Gynecological Cancer Review Group Trials Register and Cochrane Central Register of Controlled Trials) was performed for English

language studies published between January 1985 and July 2014. Search terms used were; uterine cancer, endometrial carcinoma, laparoscopy, robotic surgery, computer assisted surgery, minimally invasive surgery and gynecology.

RCTs, prospective and retrospective comparative observational studies and case–control studies comparing minimally invasive to open approach as well as laparoscopic to robotic techniques were included. For adverse outcomes and treatment side effects, non-comparative studies and case series were reviewed.

Laparoscopic surgery for endometrial carcinoma

In 1901, George Kelling was the first to attempt laparoscopy. 86 years later, laparoscopy was introduced into gynecological surgery as a tool for pre-surgical evaluation [4]. In 1992, Nezhat et al. [5] described pelvic and para-aortic lymph node dissection and laparoscopic radical hysterectomy for cervical cancer. A year later, Childers et al. [6] presented their experience with laparoscopic lymphadenectomy of pelvic and para-aortic lymph nodes for staging of endometrial cancer.

Laparotomy has some obvious advantages compared to laparoscopy; maximal surgical exposures, three-dimensional vision, direct tissue palpa-tion and manipulation and ease of suturing. Still, laparoscopic surgery is gaining importance in gynecologic oncology, and particularly in early stage endometrial carcinoma [7]. At least nine Randomized Controlled Trials (RCT) comparing laparotomy to laparoscopy, assessing more than 3,500 patients, have shown superiority or at least non-inferiority of laparoscopy compared to laparotomy in endometrial carcinoma patients [8]. Table 1 summarizes systematic reviews that analyzed these RCTs [8–11].

Laparoscopic operating room time was found to be longer but the post-operative hospital stay was significantly shorter. The higher rate of intra-operative complications observed in patients who had laparoscopy, as reported in some RCTs, could be attributed to insufficient technical skills and longer learning curve. Interestingly, more than half of patients included in most of the systematic reviews were derived from the 2009 GOG -LAP2 trial. This RCT compared 1,696 patients randomly assigned to laparoscopy surgical uterine carcinoma staging to 920 patients assigned to laparotomy staging [8, 12]. Some of these patients were enrolled as far back as 1996, when there was little experience with laparoscopic approach. The intra-operative complication rate for laparoscopy was increased in this study, thus because of the large sample size, it influenced the relative rate of intra-operative complications in almost all systematic reviews. Baring that in mind, the rate of significant intra-operative complications such as bladder, ureter, bowel and vascular injuries was almost equal in the two methods. The statistically significant but minimal difference in blood loss (about 107 ml) is supported by an equal need for blood transfusion [9].

Table 1 Summary of meta-analyses comparing laparotomy and laparoscopy for the staging of endometrial carcinoma

Category	Laparotomy	Laparoscopy
Intra-operative complications		↑
Operating room time		↑
Bladder, Ureter, Bowel, Vascular injury	=	=
Estimated blood loss	↑	
Post-operative decrease in Hemoglobin	↑	
Blood transfusion rate	=	=
Lymph node count- total	=	=
Number of Pelvic LN obtained	=	=
Detection of advanced stage disease	=	=
Post-operative hospital stay	↑	
Early post op complications[a]	↑	
Peri-operative death (within 30 days)	=	=
Moderate to Severe late post-operative adverse events[b]	↑	
Quality of life 6 weeks after surgery		↑
Recurrence free survival	=	=
3 year Recurrence rate	=	=
5 year Overall survival	=	=
Site of recurrence	=	=
Death of cancer	=	=

[a] Urinary tract infection, vaginal stump infection, hematoma, ileus, deep vein thrombosis, wound infection, wound dehiscence and temperature >38 °C

[b] Pelvic pain, urinary incontinence, prolapse, nerve injury, lymphedema, incisional hernia, deep vein thrombosis, pulmonary embolus

Total and pelvic lymph node yields, and the detection rate of advanced stage disease are markers for surgical completion. No significant difference was found in these categories. This suggests that the laparoscopic approach does not compromise the adequacy of staging and cytoreduction in endometrial carcinoma patients [13]. Data on para-aortic lymphadenectomy and the number of lymph nodes retrieved were scarce and biased from heterogeneity. In trials that para- aortic lymph node dissection was described, no difference in the lymph node counts was noticed between the two approaches [14].

Previously, concerns were raised regarding increasing the rate of cancer recurrence with laparoscopy. The published recurrence and survival results of the GOG–LAP2 study [15] demonstrate that the laparoscopic approach does not adversely affect the overall survival, recurrence free survival, recurrence rate or the patterns of recurrent disease. Thus, comprehensive surgical staging of endometrial cancer can be performed laparoscopically with a negligible difference in recurrence rates (estimated difference at

3 years, 1.14 %). Finally, laparoscopy has significant advantages compared to laparotomy in the post-operative period. In addition to a shorter hospital stay, the rate of early and late post-operative complications is lower with laparoscopy leading to faster recovery and superior quality of life [16].

Obesity

Obesity is one of the most important risk factors for endometrial carcinoma. Obese patients frequently have other co-morbidities, i.e., diabetes mellitus, hypertension and/or coronary heart disease. Morbid obesity is considered by some to be a relative contraindication to laparoscopic surgery. Of particular concern are cardiopulmonary compromise and difficulties with ventilation resulting from increased intra-abdominal pressure [17]. These impediments may prevent the steep Trendelenburg position sometimes necessary to complete the operation, limit the available operating time and increase the rate of conversion to laparotomy. In open abdominal surgery, obesity and diabetes mellitus are associated with significantly higher peri-operative complication rates such as longer surgery durations, more blood loss and higher transfusion rates. Post-operative complications, like wound infection and dehiscence or symptomatic ileus are also increased. Finally, due to prolonged hospital stay, the risks of thrombosis and pulmonary embolism rates are higher in obese patients [18]. Conversely, others recommend laparoscopy over laparotomy in obese patients to minimize these peri- and post-operative complication [19]. Vaginal procedures already provide the advantages of reducing total surgery duration and peri-operative surgical and anesthetic morbidity. However, during vaginal surgery, neither nodal nor abdominal staging can take place. Vaginal approach may be limited by anatomical circumstances as well as patients' parity [20]. Therefore, laparoscopy, even with its limitations, constitutes a valid surgical procedure in obese women. Peritoneal access restrictions, difficulty accessing the pelvic organs and performing adequate lymphadenectomy as well as the aforementioned anesthetic complications are all associated with a proportional increase in conversion rate to laparotomy with increasing BMI. However, there is no consensus for an upper limit above which laparoscopy should not be considered. The decision is almost entirely surgeon dependent and relies on the experience acquired over the years [21].

Elderly patients

Trendelenburg position and high intra-abdominal pressure could be challenging for elderly patients. Minimally invasive procedures were shown to reduce peri-operative complications such as myocardial infarction, deep vein thrombosis and pneumonia without a significant increase in operative time, blood loss or length of hospital stay. Therefore, laparoscopic staging for endometrial cancer is safe and feasible in the elderly population [22, 23].

Conversion to laparotomy

Conversion from laparoscopy to laparotomy may be necessary to complete a staging procedure or prevent an irreversible deterioration in patients' condition. Higher conversion rates are associated with widespread metastatic disease, increasing BMI and increasing patient age. The most common reason for conversion is insufficient visualization caused by inability to maintain adequate Trendelenburg position. Additional reasons are either anatomical difficulties such as dense adhesions and uterus too large to remove through the vaginal canal or management of intra-operative complications. Consequently, there is a wide range of reported conversion rates depending on patients' age, BMI, stage of disease and surgeons' expertise. Walker et al. [12] reported that 25.8 % of the patients in LAP 2 study had to be converted to laparotomy, whereas there were no conversions in the study conducted by Zullo et al. [11]. Fanning et al. [24] reviewed 235 laparoscopic procedures for endometrial cancer. In their series, 3 % of the cases were converted to laparotomy or vaginal hysterectomy.

Vaginal cuff recurrence and Port-site metastasis

During laparoscopic staging, the cancer-affected uterus and adnexa are removed through the vagina, which may raise a concern for increased vaginal cuff recurrence. Fortunately, no statistically significant difference in the rate of vaginal vault recurrence was noticed between the laparoscopic and abdominal approaches [15].

Some have stipulated that the use of intra-uterine manipulator during laparoscopic staging may contribute to dissemination of malignant cell from the uterine cavity through the fallopian tubes into the pelvic cavity.

Iavazzo et al. [25] reviewed the pertinent literature and found that the application of uterine manipulators has no clear correlation with the recurrence of the endometrial carcinoma, but the existing six trials were of low methodological quality. Hence, several authors advocate sealing the tubes at the start of the case and reduce movement of the intra-uterine manipulator to the essential minimum.

There have been a number of reports of port-site metastasis after laparoscopic treatment of endometrial cancer [26]. In most of the cases, it is attributed to initial under-staging of miliary or microscopically disseminated endometrial carcinoma and not to laparoscopy per se. In

LAP2 study [15], particular attention was given to trocar site recurrences. Only 4/1696 (0.24 %) trocar sites recurrences were identified. Three of these cases were grade 2 endometrioid adenocarcinomas stages IB, IIIA and IIIC, and one additional case was stage IVB carcinosarcoma. 3/4 presumed trocar site recurrences occurred in patients with advanced disease.

Robotic surgery for endometrial carcinoma

An ever-increasing number of endometrial carcinoma patients are being treated by minimally invasive techniques [27]. Yet, many surgeons find the laparoscopic approach difficult for routine clinical use because of increased operating time and a protracted learning curve. To facilitate the implementation of minimally invasive surgery and overcome the limitations of available laparoscopic instrumentation, a computer-controlled system that assists the surgeon in the utilization and manipulation of surgical instruments was developed. In April 2005, FDA approved the currently only available surgical robotic system (Da Vinci® Surgical System, Intuitive Surgical, Inc., Sunnyvale, CA, USA) for gynecologic laparoscopic procedures. Over the following years, robotic-assisted surgery rapidly gained acceptance by surgeons as an effective device for performing hysterectomy with staging lymphadenectomy in the management of endometrial cancer. It is estimated that in the US during 2010, more than 50 % of endometrial carcinoma staging procedures were managed with robotic-assisted surgery, representing a paradigm shift towards minimally invasive surgery not previously achieved with traditional laparoscopy. This trend expected to continue as more systems are installed worldwide and more surgeons are trained to use this platform [28]. Robotic surgery has significant technical advantages and some disadvantages compared to conventional laparoscopy [4, 29–31]: advantages include 3D visualization of the operative field, a better dexterity that mimics the freedom of human hand and wrist motion and altogether improved ergonomics for the surgeon. Disadvantages are mainly lack of tactile perception and increased cost.

The excellent 3D/HD visualization and recording of the robotic console can be used to delineate step-by-step and standardize complex surgical procedures thus ensure surgical procedure reproducibility and guarantee valid comparison between different surgeons [32, 33]. High Definition DVDs and live demonstrations via HD screens are paramount to the education of current and future gynecological oncologists.

Despite the potential benefits, there have been no prospective RCTs comparing laparotomy, laparoscopic and robotic-assisted laparoscopic staging procedures for treatment of uterine malignancies. The available studies have been relatively small in size, nonrandomized and limited to highly experienced surgeons and centers. Still, these studies are informative and demonstrate the feasibility of this technique, its safety and efficacy [34].

Table 2 Summary of meta-analyses comparing laparotomy, laparoscopy and robotic surgery for the staging of endometrial carcinoma

Category	Laparotomy	Laparoscopy	Robotic
Operative time	↓	=	=
Blood loss	↑↑	↑	↓
Transfusion rate	↑	=	=
Bladder, Ureter, Bowel, Vascular injury	=	=	=
Conversion to laparotomy		↑	↓
Number of lymph nodes	=	=	=
Hospital stay	↑	=	=
Peri-operative complications	=	=	=
Post-operative complications	↑	=	=
Re-admission rate	↑	=	=
Vaginal cuff dehiscence	↓	↑	↑

The bulk of retrospective case series and two meta-analyses (eight and nine comparative studies, 1,591 and 1,640 total patients, respectively) [34, 35] indicate similarities with laparoscopy in most categories, except for reduced blood loss and fewer conversions to laparotomy in robotic surgeries (Table 2). However, the difference in the incidence of blood transfusion between the two techniques did not reach statistical significance. Therefore, the clinical implication of this finding is questionable.

Robotic and traditional laparoscopic surgery have better outcomes than laparotomy in terms of blood loss, blood transfusions, peri and post-operative complications, wound infection, post-operative pain, shorter recovery time and decreased length of hospital stay. Pelvic and para-aortic lymph node counts, which are a measure of surgical quality, were similar for the three modalities.

The advantages of robotic surgery for the patient compared with traditional laparoscopy are not always evident [4]. Currently, it seems that robotic surgery is probably neither safer nor better than laparoscopy but allows surgeons experienced in minimally invasive approach more types of radical surgery due to its significant ergonomic advantages [29, 31]. For the surgeons inexperienced in laparoscopy, computer assisted surgery enables to execute complex procedures more easily.

Disadvantages include costs associated with purchasing the robotic system and disposable equipment, loss of haptic sensation and the lack of accessibility for all patients with appropriate indications. Operative times for robotic and laparoscopy cases are similar, but longer than that for laparotomy cases [36].

Taking into account various reimbursement systems in different countries, recent cost analyses studies indicate that the shorter operating times and the efficiencies gained with robotic surgical experience may translate into significant reductions in operating room costs, such that the widely held belief that robotic surgery is 'too expensive' may not be true for many institutions [37, 38].

Finally, three recently published retrospective survival analyses of combined 1,054 [39–41] patients provide evidence that robotic-assisted laparoscopy for endometrial carcinoma has similar overall and recurrence free survival rates to traditional laparoscopy and laparotomy.

Vaginal vault dehiscence

Concerns regarding increasing incidence of vaginal vault dehiscence following robotic surgery were raised. Drudi et al. [42] estimated a low vaginal vault dehiscence incidence after abdominal staging (0.12 %) while slightly elevated and almost similar incidence following laparoscopy and robotic surgery (1.1–4.9 % and 0.7–2.6 %, respectively). Compared to traditional laparoscopy, no technique specific etiology could be identified. Among the contributing factors to vaginal dehiscence are: patients' risk factors for delayed healing such as vaginal atrophy and infection, steroid use and application of chemotherapy and/or radiotherapy, vaginal cuff thermal injury by electrocautery and vaginal coitus with deep penetration prior to 12 weeks after surgery.

Obesity

The challenges associated with operating obese (BMI 30–39) and morbidly obese (BMI > 40) patients are almost identical for robot assisted and traditional laparoscopy namely, exposure during aortic lymph node dissection and adequate ventilation during steep Trendelenburg positioning. Contrary to traditional laparoscopy, modifying the Trendelenburg positioning during robotic surgery is impossible without un-docking the robotic arms, thus extending the operative time. Yet, Menderes et al. [43] believe that the robotic platform enhances the laparoscopic skills of the operator necessary when the patient has a challenging body habitus and that obese and morbidly obese patients could be good candidates for robotic surgery [44].

Much like traditional laparoscopy, robotic surgery reduces peri and post-operative complications, particularly abdominal wound complications, while maintaining adequate pelvic and para-aortic lymph node retrieval counts, overall survival and recurrence rates when compared to open surgery. However, Holloway et al. [28] showed that robotic lymph node yields in obese patients were greater than those of laparoscopic cases, node counts for morbidly obese patients were not greater than laparoscopy, indicating that robotic aortic lymphadenectomy may still have some limitations for this group of difficult patients.

Elderly patients

Detailed information regarding robotic surgery in elderly and high anesthesiological risk endometrial carcinoma patients is scarce. Lavoue et al. [45] showed that robotic staging of elderly (age ≥ 70) endometrial carcinoma patients is feasible and associated with significant benefits compared to open surgery, including lower minor complication rate, less operative blood loss and shorter hospitalization without compromising 2-year disease-free survival. The traditional reluctance to perform radical robotic surgery in medically ill women is not supported by adequate evidence. Siesta et al. [46] examined robotic staging in 66, ASA ≥ 3 endometrial and cervical carcinoma patients. They concluded that comprehensive robotic staging is feasible and safe in these patients.

Conclusion

In the recent years, gynecologists have come to realize that there is more than one way to perform staging and hysterectomy for endometrial carcinoma. RCT based evidence indicates that laparoscopic staging is similar to laparotomy with regard to surgical completion, adequacy of staging and cytoreduction, survival and recurrence rates. Yet, patients undergoing laparoscopic staging or laparoscopic hysterectomies still comprise only a small percentage of all hysterectomies in the US and around the world [38]. Robotic platform overcomes some of the limitations of standard laparoscopic instrumentation and has increased the accessibility of gynecologists to minimally invasive techniques. Therefore it is not surprising that in a short period, computer assisted laparoscopic staging has gained an unprecedented popularity amongst gynecological oncologist. Based on retrospective reports, robotic surgery for endometrial carcinoma is at the least non-inferior to laparotomy and traditional laparoscopy with respect to adequacy of staging, post-operative complications and overall and recurrence free survival rates. Robotic surgery has the advantage of lower rate of conversion to laparotomy and lower blood loss. Thus, minimally invasive approach should be considered to be the surgical treatment option of choice in endometrial carcinoma patients.

Leitao [47] argued that the evolution in the minimal invasive treatment of endometrial carcinoma has transformed into an uncontrolled revolution based on single institution retrospective studies. Berchuck et al. [48]

contend that "the horse is already out of the barn" and minimally invasive surgery, especially robotic surgery, for endometrial cancer has become the dominant paradigm. Many surgeons bypass laparoscopy in favor of robotic surgery because it is easier to master, less dependent on the availability of a trained assistant, and has ergonomic advantages for the surgeon. Robotic surgery may be particularly helpful in obese patients but at least for now, more expensive than the other modalities.

Minimally invasive surgical techniques continue to evolve as the next generation of robotic platforms which integrate tactile feedback and single-port laparoscopic and robotic instruments are being tested [16].

The goal of all gynecologic cancer surgeons should be to perform surgery in a way that minimizes disfigurement and psychological trauma and preserves function. Innovative methods and instruments, such as the robotic platform, sentinel lymph node biopsy and single-port surgery must continue to evolve as technology advances.

Conflict of interest Author(s) declare no conflict of interest.

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