Minimally Invasive Surgery for Endometrial Cancer

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S.P. Somashekhar

Abstract

Objectives in improving cancer treatment can be categorized as those that improve efficacy and those that lessen morbidity.

Minimally invasive surgery seeks to decrease morbidity from surgery while maintaining at the very least equivalent efficacy. Laparoscopic method is established as a standard technique with the landmark trial of GOG LAP2.

Robotic approach further enhances the benefits of laparoscopy with similar results especially in obese women. However, randomized trials are awaited in this regard. Early case series thus far reported suggest robotic surgery for endometrial cancer is feasible.

Main advantages of robotic technology over laparoscopy include 3D vision with better camera, more flexible instruments, less conversion rate, ease of surgery, surgeon's comfort, and shorter learning curve.

Current limitations of robotic surgery are mostly due to mechanical/energy source-related instrument problems, high cost, and longer operating time.

The extent of surgery depends on the stage and extent of disease.

Adjuvant treatment is offered based on surgical stage and adverse factors.

Chemoradiation shows promising results in high-risk and advanced-stage disease.

Systemic treatment of metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy.

S.P. Somashekhar, MS, MCh (Onco), FRCS.Edinburgh
Manipal Comprehensive Cancer Center, Manipal Hospital,
HA-Airport road, Bangalore 560017, India
e-mail: somusp@yahoo.com

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Introduction

Endometrial cancer is the sixth most common malignancy among females worldwide. In developed countries, endometrial cancer is the fourth most common cancer in women [1]. Endometrial cancer is common in western women, and the rates are very high; however, in India, the rates are as low as 4.3 per 100,000 (Delhi) [2]. More than 90 % of cases occur in women older than 50 years of age, with a median age of 63 years. Chronic estrogen exposure is the most common risk factor followed by genetic predisposition (10 %), e.g., HNPCC/Lynch syndrome and chronic liver disease like cirrhosis. Most cases of endometrial cancer are diagnosed in early stages since abnormal uterine bleeding is the presenting symptom in 90 % of cases.

Endometrial cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO 2009) system [3]. Preoperative imaging is not mandatory. Dynamic contrast-enhanced magnetic resonance imaging (MRI) is the best tool to assess the cervical involvement [4, 5]. In a few studies, MRI has been shown to accurately evaluate the depth of myometrial invasion. A prospective collaborative trial, comparing MRI and ultrasonography (US), reported that the accuracy of US is comparable to that provided by MRI [6], but US is highly operator dependent. CA-125 marker is raised in extrauterine disease and is a bad prognostic marker.

Multiple factors have been identified for high risk of recurrence in apparent early-stage disease: histological subtype, grade 3 histology, myometrial invasion ≥50 %, lymphovascular space invasion (LVSI), lymph node metastases, and tumor diameter >2 cm. In this regard, stage I can be subdivided into three risk categories:

Low risk: stage IA (G1 and G2) with endometrioid type
Intermediate risk: stage IA G3 with endometrioid type and stage IB (G1 and G2) with endometrioid type
High risk: stage IB G3 with endometrioid type, all stages with non-endometrioid type

Two main clinicopathological types of endometrial cancer have been recognized, corresponding to estrogen-dependent, more common endometrioid (type 1) and estrogen-independent non-endometrioid carcinomas (type 2). Type 2 endometrial cancer carries bad prognosis. Both type 1 and type 2 have different etiopathogenesis through different molecular pathways. Unlike typical (or "prototypical") tumors, several cases still remain morphologically ambiguous, indeterminate, or hybrid adenocarcinomas, requiring immunohistochemistry (ER, PR, p53, p16, PTEN) and eventually mutational analysis to allow for a correct interpretation.

Surgical Treatment

The surgical approach for the treatment of endometrial cancer has traditionally been laparotomy. Nevertheless, in the last 15 years, the use of minimally invasive techniques has been widely accepted by many authors. A recent publication of the

Gynecologic Oncology Group (GOG) LAP2 study has shown similar operative outcomes in the minimally invasive surgery and in the laparotomy group. Laparoscopy seems to provide equivalent results in terms of disease-free survival and overall survival compared with laparotomy, with further benefits: shorter hospital stay, less use of pain killers, lower rate of complications, and improved quality of life. A potential enhancement to laparoscopy has been provided by the robotic approach with a high "benefit" in obese women. Since 2002, the use of robotic-assisted laparoscopy has advanced rapidly, particularly in the United States. The largest published series of robotic surgery was reported in 2011 by Paley et al. [10]. The major complication rate was significantly less with robotic surgery (20 % vs. 6.4 %) compared with laparotomy, particularly related to wound complications and infections.

Surgical Treatment in Stage I Endometrial Cancer

The standard surgical approach for stage I endometrial cancer consists of total hysterectomy and bilateral salpingo-oophorectomy (BSO) with or without lymphadenectomy [I, A]. Lymphadenectomy could be important in determining a patient's prognosis and in tailoring adjuvant therapies. Hence, many authors suggest a complete surgical staging for intermediate high-risk endometrioid cancer (stage IA G3 and IB) [II, B]. Randomized trials have failed to show a survival or relapse-free survival benefit in stage I endometrial cancer [I, A], and the role of systematic pelvic lymphadenectomy is an issue of current debate. In an Italian study, 514 patients with stage I endometrial cancer were randomized to receive lymphadenectomy or not (excluding stage IA–IB G1 and non-endometrioid histotype). In this study, systematic lymphadenectomy did not improve disease-free or overall survival [11]. In the ASTEC trial, 1408 women with malignancies confined to the uterus were randomized. In this trial, there was no evidence of a benefit on overall survival or recurrence-free survival when pelvic lymphadenectomy was carried out [12]. The authors concluded that routine systematic pelvic lymphadenectomy cannot be recommended in women with stage I endometrial cancer, unless enrolled in clinical trials. However, the design of these studies has not addressed the most important impact of lymphadenectomy in the high-risk population in order to identify patients who can safely avoid or benefit from adjuvant treatment. A large retrospective study published in 2010, comparing systematic pelvic lymphadenectomy vs. systematic pelvic and para-aortic lymphadenectomy (SEPAL) study, has suggested that overall survival was significantly longer in patients undergoing pelvic and para-aortic lymphadenectomy [13]. The SEPAL study suggests that high-risk patients may benefit from aggressive surgery. Sentinel lymph node identification in endometrial cancer has been described with interesting preliminary results, which deserve further investigation in properly designed clinical studies. Further randomized trials will be focused on investigating the role of lymphadenectomy for patients with high-risk endometrial cancer to direct subsequent treatment and the role of sentinel node biopsy.

Surgical Treatment in Stage II Endometrial Cancer

Traditionally, the surgical approach consists of radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy. In stage II, lymphadenectomy is recommended to guide surgical staging and adjuvant therapy.

Robotic-Assisted Surgery for Endometrial Cancer

The benefits of robotic surgery as a minimally invasive surgical technique parallel those of traditional laparoscopy, with the added advantages of overcoming several barriers to the use of laparoscopy.

Basics of Robot

Surgeon performs surgery using a computer that remotely controls very small instruments attached to the robot. It allows surgeons to perform delicate operations by manipulating the robotic arms, which translate the surgeon's hand movements into smaller and smoother strokes. It has revolutionized the field of surgery by allowing the surgeon to perform less-invasive and complex surgical procedures that were once only possible with open surgery. Robotic machine has three parts – surgeon's console (Fig. 7.1), patient cart (Fig. 7.2), and optical cart. Surgeon's console contains 3D monitor and joysticks which control the instruments. Patient cart has four arms for the instrument and camera. With changing technology, improved versions of robot have better surgeon's console and patient cart.

Robotic surgery enables surgeons to be more precise, advancing their technique and enhancing their capability in performing complex minimally invasive surgery.

Binocular stereoscopic 3D vision with stability of camera and 10× magnification allows the surgeon better visualization of the anatomy, which is especially critical when working around delicate and confined structures like in the pelvis, chest, or abdomen. This allows surgeons to perform radical cancer surgeries with superior oncological outcome.

It mimics the human hand in its flexible movement and also overcomes limitations of it, like 7° of movement and elimination of hand tremors. Despite the widespread use of laparoscopic surgery, adoption of laparoscopic techniques, for the most part, has been limited to a few routine procedures. This is due mostly to the limited capabilities of traditional laparoscopic technology, including standard video and rigid instruments. Surgeons have been slow to adopt laparoscopy for complex procedures because they generally find that fine-tissue manipulation such as dissecting and suturing to be more difficult. Intuitive technology, however, enables the use of robot for complex procedures. The robot allows for 7° of motion vs. the limited 4° of motion in laparoscopy. Robotic technology eliminates the fulcrum effect of laparoscopy (the robotic arms imitate the movements of the surgeon's hand).

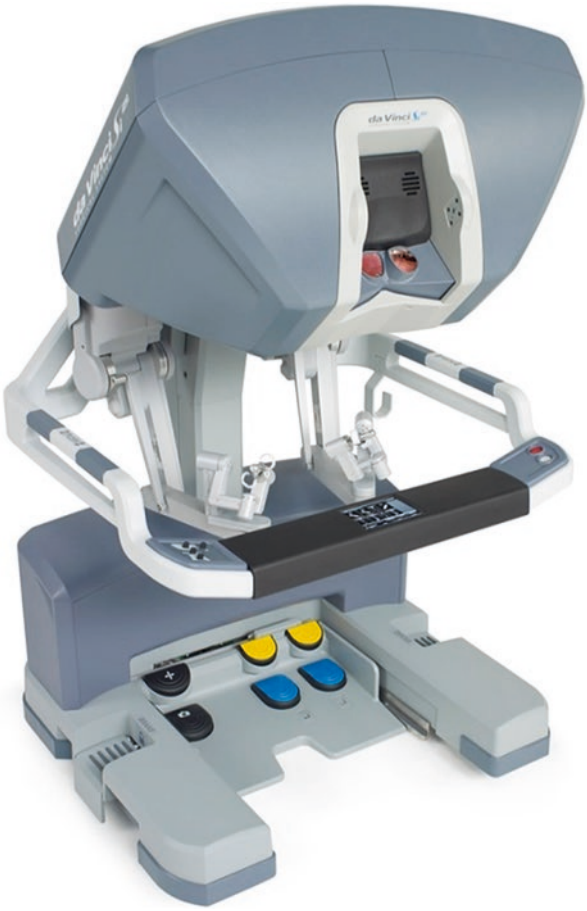


Fig. 7.1 Surgeon's console

Motion scaling and precision of surgical movements during robotic surgery improve the quality of surgery. Extremely easy and fast suturing and knotting and multitasking instrumentations decrease operative time. Surgeon sits and operates at ease with less fatigue, translating to safe surgery.

Surgical Technique

Preoperative Preparation

Patient takes clear liquids a day prior to surgery. Proctoclysis enema and two Dulcolax (bisacodyl) tablets are given per oral a night before the surgery. We do not administer Peglec which causes dilatation of the bowel.

Port placement (Figs. 7.3 and 7.4) and instrumentation (Fig. 7.8)

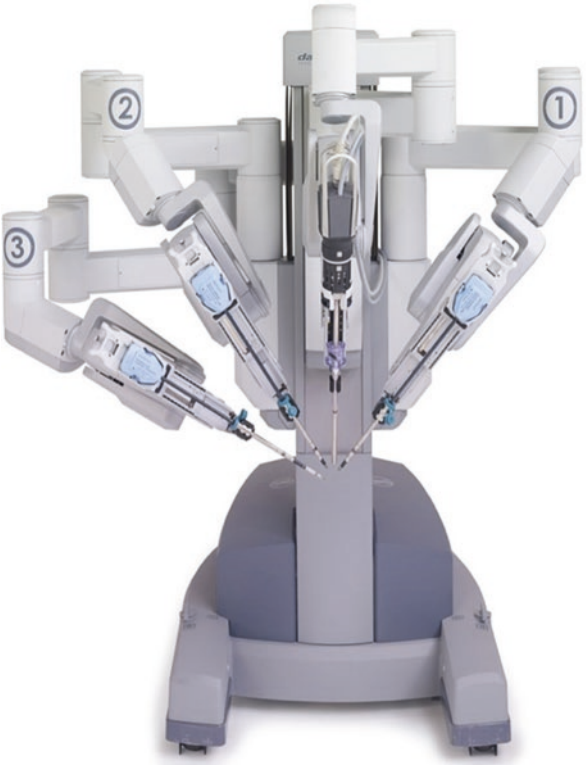


Fig. 7.2 Patient cart

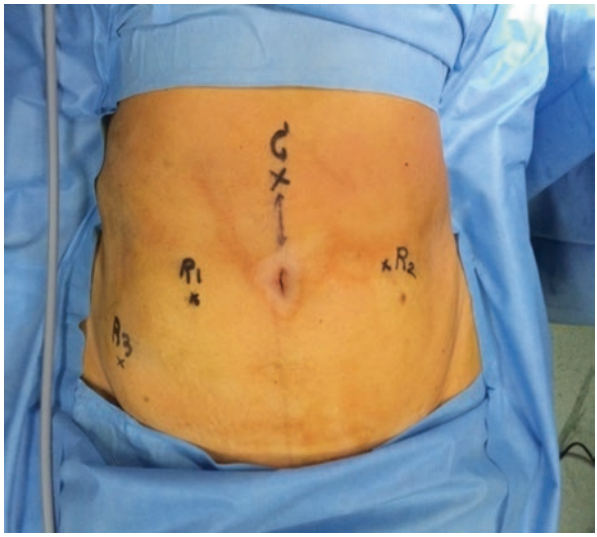


Fig. 7.3 Abdominal marking of port placement

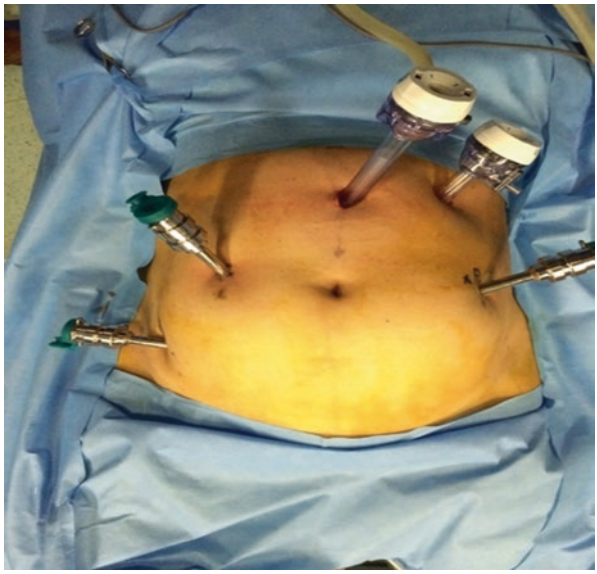


Fig. 7.4 Port placement

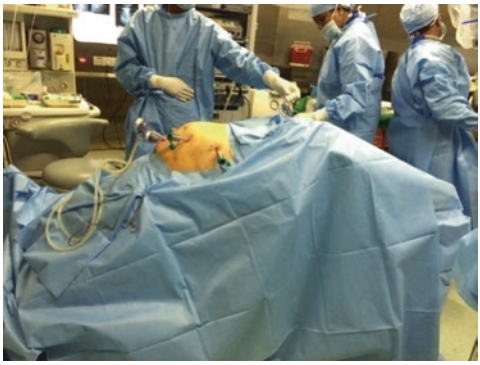
Vaginal-Cervical Ahluwalia Retractor-Elevator (VCARE) uterine manipulator is fixed to the cervix after placing patient in lithotomy position. Intraoperatively, it helps in manipulating the uterus. A 12 mm camera port is placed 3 cm above the umbilicus in the midline with optical trocar. The rest of the ports are placed after insufflating the abdomen with gas and marking the port measurements. Arm-one (8 mm) port is placed on patient's right side, 3–5 cm below and at least 8 cm lateral to the camera port. Arm-two (8 mm) port is placed on patient's left side, 8 cm lateral and 3–5 cm below the level of the camera port. Arm-three (8 mm) port is placed on patient's right side, 2 cm above the anterior superior iliac spine and 8 cm away from the first port. Assistant port (12 mm) is placed on patient's left side, slightly cephalad to the camera port on an arc at the midpoint between the camera port and the instrument arm-two port.

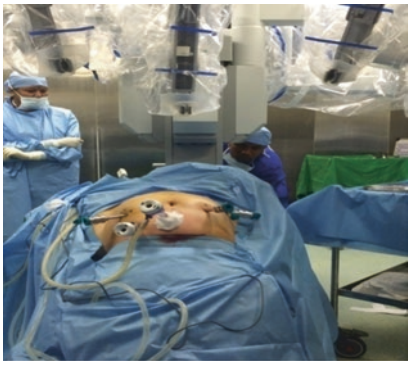
Zero-degree scope is used for all the steps, except for para-aortic lymph node dissection where 30° down scope is used. In arm-one hot shears (monopolar curved scissors), in arm-two fenestrated bipolar forceps, and in arm-three prograsp forceps is used (Figs. 7.5 and 7.6, 7.7).

After placing all the ports, the patient is positioned before docking the robot. Head end side is lowered completely, and all the bowel loops are taken toward the upper abdomen. Pelvic wash is given and fluid is taken for cytological examination (Fig. 7.8).

Surgical Steps

Dissection is done in a circular fashion from one round ligament to the other.





Figs. 7.5 and 7.6 Patient positioning and Docking in progress

Fig. 7.7 Post docking

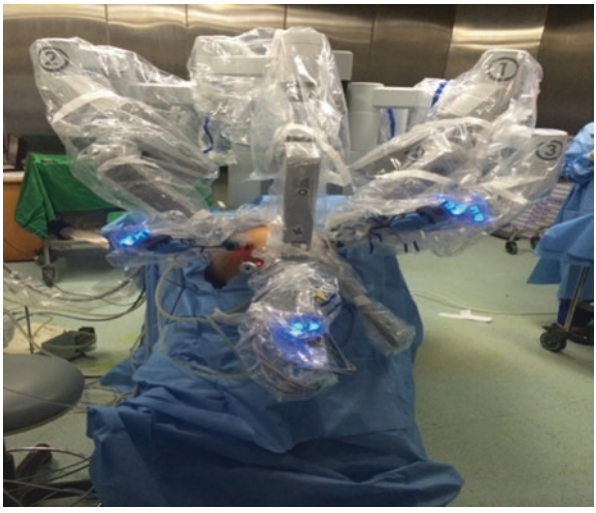
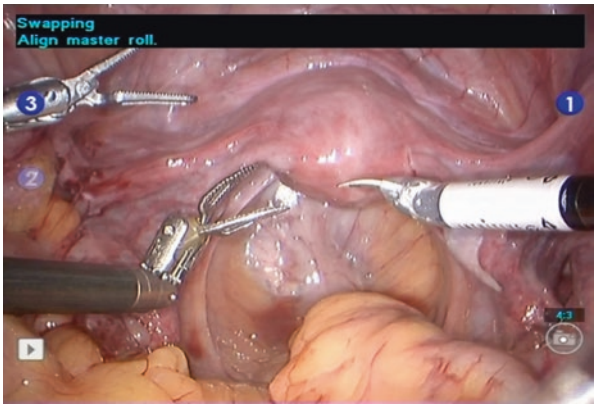


Fig. 7.8 Robotic instruments with endowrist technology



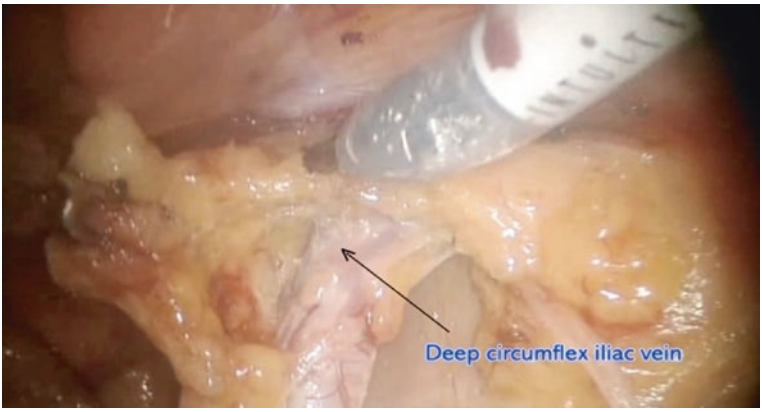


Fig. 7.9 Pelvic lymphadenectomy – distal boundary

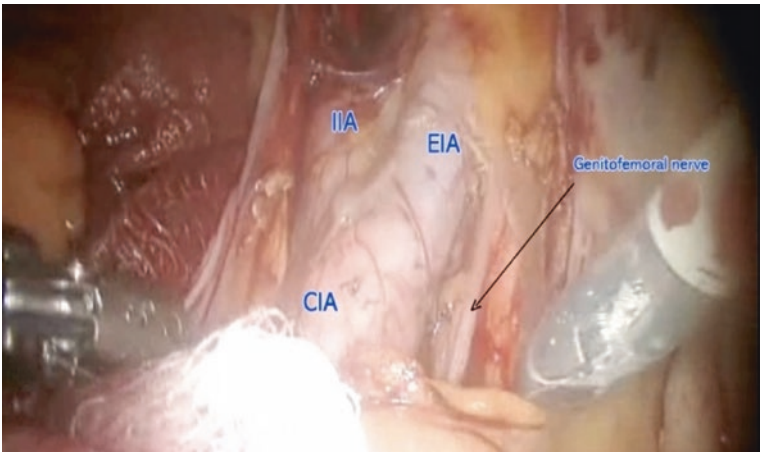


Fig. 7.10 Pelvic lymphadenectomy – lateral and proximal boundary

Step 1: The uterus is retracted to the patient's left side with the help of uterine manipulator. Dissection starts with incising the peritoneum over the infundibulopelvic triangle, isolating the ureter and ovarian pedicle. Then, the round ligament is transected near the inguinal ring with hot shear (monopolar diathermy). Incision is extended anteriorly into the anterior leaf of the broad ligament up to the lateral uterovesical junction. Coagulate and transect the right uterine pedicle and cardinal ligament. Pay careful attention to the course of the ureter.

Step 2:The urinary bladder is lifted up with third arm, and the uterus is retroverted with the help of uterine manipulator and second arm. The vesicouterine groove is identified and the bladder is dissected away from the uterus, and adhesions if any are dissected with the cold knife (hot shear).

Step 3: Left-side isolation of the ureter and dissection of the round ligament are done similar to step 1. Both side ovarian pedicles are coagulated with bipolar diathermy but not divided until complete dissection is done.

Step 4: Posterior part dissection is done by separating the rectum from the uterus with the division of the uterosacral ligaments on either side. The course of the ureter must be noted during this step.

Step 5: Anterior and posterior colpotomies are done by incising over the colpotomy ring. Finally, both the ovarian pedicles are divided. Specimen is delivered through the vagina by pulling out the uterine manipulator, and abdominal pneumatic pressure is maintained by packing the vagina with an adequate size ball made of mop inside a surgical hand glove.

Step 6: Bilateral pelvic lymphadenectomy (Figs. 7.11 and 7.12) is done by exposing the pararectal and paravesical spaces. Separate specimen bag is used for each side of the lymph nodes, and specimen is delivered through the vagina. Para-aortic lymph node dissection is done when indicated. The vaginal cuff is closed with a 15 cm long self-retaining polydioxanone (monofilament, violet) barb suture, and uterosacral ligaments are included laterally.

The role of systematic pelvic lymphadenectomy is an issue of current debate. Excision of suspicious or enlarged nodes is important to exclude metastasis. A more selective and tailored lymphadenectomy approach is now recommended to avoid systematic overtreatment [6]. No randomized trial data support full lymphadenectomy [7] although some retrospective studies have suggested that it is beneficial [8]. A subset of patients may not benefit from lymphadenectomy, but it is difficult to preoperatively identify these patients because of the uncontrollable variable of change in grade and depth of invasion in final histopathology.

As the grade of the tumor increases, accuracy of intraoperative evaluation of myometrial invasion by gross examination decreases. Therefore, frozen section examination for evaluation of the histology, size of primary, grade, and depth of invasion is important. Pending further trials, pelvic lymphadenectomy is done in all patients. Para-aortic lymphadenectomy is indicated in high-risk patients.

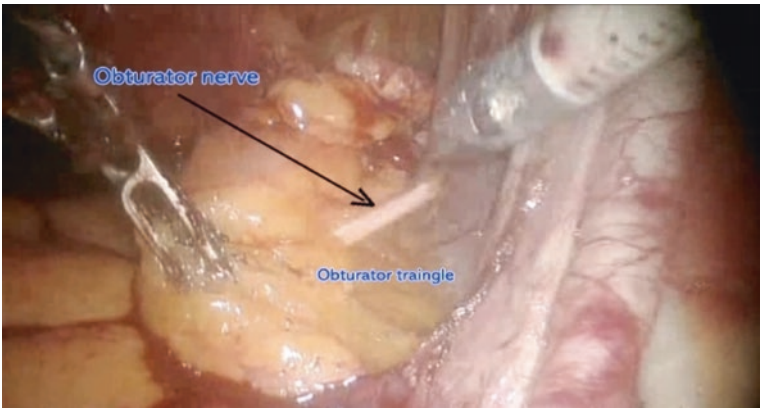


Fig. 7.11 Pelvic lymphadenectomy – inferior boundary

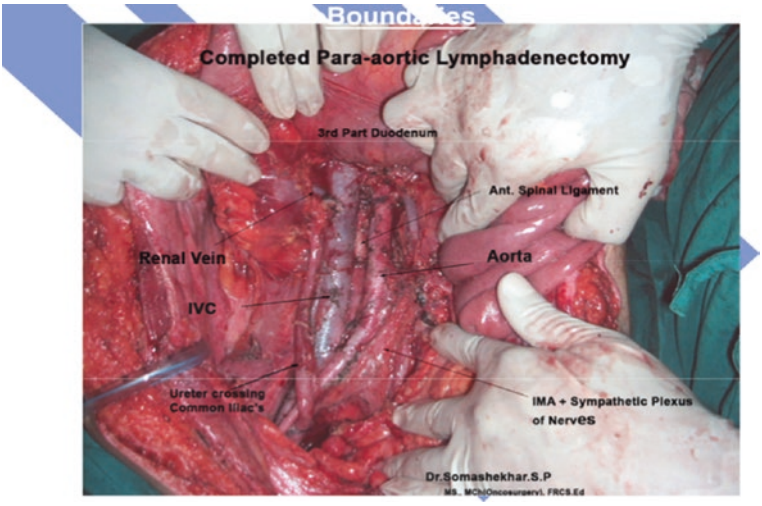


Fig. 7.12 Completed paraortic lymphadenectomy with critical structures

Anatomical spaces in pelvic dissection:

1. Paravesical space
2. Pararectal space

Anatomical boundaries:

Distal – deep circumflex iliac vein
Proximal – common iliac vessels
Laterally – genitofemoral nerve
Inferiorly – obturator fossa (Figs. 7.9 and 7.10)

Para-aortic Lymphadenectomy

Boundaries

Superiorly – renal vein
Inferiorly – common iliac vessels
Laterally – ureter

Evolving Evidence

Efficacy of Laparoscopy

The Gynecologic Oncology Group (GOG) has completed a phase III randomized study (lamina-associated polypeptide 2 (LAP2)) comparing laparoscopy vs.

laparotomy in endometrial cancer [9]. Patients with clinical stage I–IIA uterine cancer were randomly assigned to laparoscopy ($n = 1696$) or open laparotomy ($n = 920$), including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy. Laparoscopy was initiated in 1,682 patients and completed without conversion in 1,248 patients (74.2 %). Conversion from laparoscopy to laparotomy was secondary to poor visibility in 14.6 %, metastatic cancer in 4.1 %, bleeding in 2.9 %, and other causes in 4.2 %. Laparoscopy had fewer moderate to severe postoperative adverse events than laparotomy (14 % *v* 21 %, respectively; $P = .0001$) but similar rates of intraoperative complications, despite having a significantly longer operative time (median, 204 *v* 130 min, respectively; $P = .001$). Hospitalization of more than 2 days was significantly lower in laparoscopy vs. laparotomy patients (52 % *v* 94 %, respectively; $P = .0001$). They concluded that laparoscopic surgical staging for uterine cancer is feasible and safe in terms of short-term outcomes and results in fewer complications and shorter hospital stay. Time to recurrence was the primary end point, with non-inferiority defined as a difference in recurrence rate of less than 5.3 % between the two groups at 3 years. The recurrence rate at 3 years was 10.24 % for patients in the laparotomy arm, compared with 11.39 % for patients in the laparoscopy arm, with an estimated difference between groups of 1.14 % (90 % lower bound, −1.278; 95 % upper bound, 3.996) [10]. Although this difference was lower than the pre-specified limit, the statistical requirements for non-inferiority were not met because of a lower-than-expected number of recurrences in both groups. The estimated 5-year overall survival was almost identical in both arms at 89.8 %. These results, combined with previous findings from this study of improved QOL and decreased complications associated with laparoscopy, are reassuring to patients and allow surgeons to reasonably suggest this method as a means to surgically treat and stage patients with presumed early-stage endometrial cancers.

Another prospective randomized trial is ongoing at Australian and the UK institutions, the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial anticipated to randomize 590 patients to total laparoscopic hysterectomy and lymph nodal staging vs. standard, open surgery [11].

Disadvantages of laparoscopy:

- Steep learning curve
- Limited dexterity
- Counterintuitive motion
- Two-dimensional field
- Limited depth perception
- Ergonomic difficulty

Evidence for Robotic-Assisted Surgery

Obesity

Endometrial cancer is particularly suited for robotic surgery for several reasons. The majority of women with endometrial cancers are obese and at greater risk for

postoperative wound complications and would benefit from a minimally invasive procedure with smaller incisions, resulting in less risk for wound problems. However, at the same time, obesity increases the degree of difficulty of management via laparoscopy, maybe to the extent that the level of difficulty may become prohibitive in accomplishing the operation. In a retrospective comparison of obese women and morbidly obese women undergoing traditional laparoscopic approach vs. robotic-assisted approach, better surgical outcomes were observed in the group undergoing robotic-assisted laparoscopy [12]. The group who underwent the procedure robotically had significantly shorter operating time, less blood loss, improved lymph node count, and shorter hospital stay suggesting that robotic-assisted laparoscopy greatly facilitates laparoscopic surgery in obese patients. In obese patients with greater abdominal surface area, adequate spacing between the ports and in turn clashing of the arms are seldom a problem.

Bernardini et al. [13] studied women with clinical stage I or II endometrial cancer and a BMI greater than 35 kg/m^2 treated with robotic surgery at their institution between November 2008 and November 2010. These patients were compared with a historical cohort of similar patients who underwent laparotomy. A total of 86 women were analyzed in this study (robotic surgery, 45; laparotomy, 41). The overall intraoperative complication rate was 5.8 %. There was no statistical difference in age, number of comorbidities, BMI, prior abdominal surgery, and operative complications between the women who underwent robotic surgery vs. laparotomy. Postoperative complication rates were higher in the laparotomy group (44 % vs. 17.7 %; $P = 0.007$), and hospital length of stay was also higher in the laparotomy group (4 vs. 2 days; $P = 0.001$). There was no difference in rates of (pelvic) lymph node dissection; however, para-aortic node dissection was more common in the robotic surgery group.

Learning Curve

An analysis of robotic-assisted hysterectomy with lymphadenectomy vs. total laparoscopic hysterectomy with lymphadenectomy and laparotomy with total abdominal hysterectomy with lymphadenectomy was done by Lim PC et al. [14]. Data were categorized by chronologic order of cases into groups of 20 patients each. The learning curve of the surgical procedure was estimated by measuring operative time with respect to chronologic order of each patient who had undergone the respective procedure. Analysis of operative time for robotic-assisted hysterectomy with bilateral lymph node dissection with respect to chronologic order of each group of 20 cases demonstrated a decrease in operative time: 183.2 (69) min (95 % CI, 153.0–213.4) for cases 1–20, 152.7 (39.8) min (95 % CI, 135.3–170.1) for cases 21–40, and 148.8 (36.7) min (95 % CI, 130.8–166.8) for cases 41–56. For the groups with laparoscopic hysterectomy with lymphadenectomy and traditional total abdominal hysterectomy with lymphadenectomy, there was no difference in operative time with respect to chronologic group order of cases. It was concluded that the learning curve for robotic-assisted hysterectomy with lymph node dissection seems to be

easier compared with that for laparoscopic hysterectomy with lymph node dissection for surgical management of endometrial cancer.

Survival Analysis

Retrospective study was conducted at two academic centers to compare the survival of women with endometrial cancer managed by robotic- and laparoscopic-assisted surgery [15]. A total of 183 women had robotic-assisted surgery and 232 women had laparoscopic-assisted surgery. With a median follow-up of 38 months (range 4–61 months) for the robotic and 58 months (range 4–118 months) for the traditional laparoscopic group, there were no significant differences in survival (3-year survival 93.3 and 93.6 %), DFS (3-year DFS 83.3 and 88.4 %), and tumor recurrence (14.8 and 12.1 %) for robotic and laparoscopic groups, respectively. Univariate and multivariate analysis showed that surgery is not an independent prognostic factor of survival. Robotic-assisted surgery yields equivalent oncological outcomes when compared to traditional laparoscopic surgery for endometrial adenocarcinoma.

A retrospective chart review was performed for all consecutive endometrial adenocarcinoma patients surgically staged with robotic-assisted laparoscopy at the University of North Carolina Hospital from 2005 to 2010 [16]. Demographic data, 5-year survival, and recurrence-free intervals were analyzed. Surgical staging was 85.2 % for stage IA, 80.2 % for stage IB, 69.8 % for stage II, and 69 % for stage III. Projected 5-year survival was 88.7 % for all patients included in the study. Nearly 82 % of cases were endometrioid adenocarcinoma, with papillary serous, clear cell, or mixed histology comprising 17.4 % of cases. Median follow-up time was 23 months, with a range of 0–80 months. Among stage IA, IB, II, and III patients, projected overall survival was 94.2 %, 85.9 %, 77.4 %, and 68.6 %, respectively. The results from this study demonstrate that robotic-assisted surgical staging for endometrial cancer does not adversely affect rates of recurrence or survival. These findings provide further evidence that robotic-assisted laparoscopic surgical staging is not associated with inferior results when compared to laparotomy or traditional laparoscopy.

Advantages of robotic technology:

- Binocular stereoscopic 3D vision.
- Stable, high-definition camera with 10× magnification.
- EndoWrist instrumentation – increased dexterity.
- Extremely easy and fast suturing and knotting intracorporeally.
- Surgeons sit and operate at ease with arms rested.
- Multitasking instrumentations.
- Option of harmonic scalpel.
- Three arms in addition to camera arm.
- Filters human tremor.
- Ergonomic with equal access with both left- and right-sided ports.

Efficacy of Robotic Surgery

In our prospective randomized study [17] of 50 consecutive patients with carcinoma endometrium, estimated blood loss (81.28 ml), hospital stay (1.94 days), and perioperative complications were significantly less in robotic-assisted group in comparison to open method. Mean number of lymph nodes removed were 30.56 vs. 27.6 which is suggestive of significant difference statistically. Operative time decreased as the experience of the surgeon increased but still significantly remained higher than the open procedure after 25 robotic-assisted surgeries. All robotic surgeries were completed successfully without converting to open method. Robotic-assisted staging procedure for endometrial cancer is feasible without converting to open method, with the advantages of decreased blood loss, short duration of hospital stay, and less postoperative minor complications.

A cohort study [18] was performed by prospectively identifying all patients with clinical stage I or occult stage II endometrial cancer who underwent robotic hysterectomy and lymphadenectomy from 2006 to 2008 and retrospectively comparing data using the same surgeons' laparoscopic hysterectomy and lymphadenectomy cases from 1998 to 2005, prior to their robotic experience. Patient demographics, operative times, complications, conversion rates, pathologic results, and length of stay were analyzed. One hundred and eighty-one patients (105 robotic and 76 laparoscopic) met inclusion criteria. There was no significant difference between the two groups in median age, uterine weight, bilateral pelvic or aortic lymph node counts, or complication rates in patients whose surgeries were completed minimally invasively. Despite a higher BMI (34 vs. 29, $P < 0.001$), the estimated blood loss (100 vs. 250 ml, $P < 0.001$), transfusion rate (3 % vs. 18 %, RR 0.18, 95 % CI 0.05–0.64, $P = 0.002$), laparotomy conversion rate (12 % vs. 26 %, RR 0.47, 95 % CI 0.25–0.89, $P = 0.017$), and length of stay (median 1 vs. two nights, $P < 0.001$) were lower in the robotic patients compared to the laparoscopic cohort. The odds ratio of conversion to laparotomy based on BMI for robotics compared to laparoscopy is 0.20 (95 % CI 0.08–0.56, $P = 0.002$). The mean skin to skin operating time (242 vs. 287 min, $P < 0.001$) and total room time (305 vs. 336 min, $P < 0.001$) was shorter for the robotic cohort. It was concluded that robotic hysterectomy and lymphadenectomy for endometrial cancer can be accomplished in heavier patients and result in shorter operating times and hospital length of stay, lower transfusion rate, and less frequent conversion to laparotomy when compared to laparoscopic hysterectomy and lymphadenectomy.

Magrina et al. [19] did a prospective analysis of 67 patients undergoing robotic surgery for endometrial cancer between March 2004 and December 2007. Comparison was made with similar patients operated between November 1999 and December 2006 by laparoscopy (37 cases), laparotomy (99 cases), and vaginal/laparoscopy approach (vaginal hysterectomy, bilateral adnexectomy/laparoscopic lymphadenectomy) (47 cases) and matched by age, body mass index (BMI), histological type, and International Federation of Gynecology and Obstetrics (FIGO) staging. Mean operating times for patients undergoing robotic, laparoscopy, vaginal/laparoscopy, or laparotomy approach were 181.9, 189.5, 202.7, and 162.7 min,

respectively ($p = 0.006$); mean blood loss was 141.4, 300.8, 300.0, and 472.6 ml, respectively ($p < 0.001$); mean number of nodes was 24.7, 27.1, 28.6, and 30.9, respectively ($p = 0.008$); and mean length of hospital stay was 1.9, 3.4, 3.5, and 5.6 days, respectively ($p < 0.001$). There were no significant differences in intra- or postoperative complications among the four groups. The conversion rate was 2.9 % for robotic and 10.8 % for the laparoscopy group (0.001). There were no differences relative to recurrence rates among the four groups: 9 %, 14 %, 11 %, and 15 % for robotics, laparoscopy, vaginal/laparoscopy, and laparotomy, respectively. It was concluded that robotics, laparoscopy, and vaginal/laparoscopy techniques are preferable to laparotomy for suitable patients with endometrial cancer. Robotics is preferable to laparoscopy due to a shorter hospital stay and lower conversion rate and preferable to vaginal/laparotomy due to a reduced hospitalization.

Ran et al. recently reported a meta-analysis which included 22 studies [20]. These studies involved a total of 4420 patients, 3403 of whom underwent both robotic surgery and laparoscopy and 1017 of whom underwent both robotic surgery and laparotomy. The estimated blood loss ($p = 0.01$) and number of conversions ($p = 0.0008$) were significantly lower, and the number of complications ($p < 0.0001$) was significantly higher in robotic surgery than in laparoscopy. The operating time (OT), length of hospital stay (LOHS), number of transfusions, and total lymph nodes harvested (TLNH) showed no significant differences between robotic surgery and laparoscopy. The number of complications ($p < 0.00001$), LOHS ($p < 0.00001$), EBL ($p < 0.00001$), and number of transfusions ($p = 0.03$) were significantly lower, and the OT ($p < 0.00001$) was significantly longer in robotic surgery than in laparotomy. The TLNH showed no significant difference between robotic surgery and laparotomy. Conclusions: Robotic surgery is generally safer and more reliable than laparoscopy and laparotomy for patients with endometrial cancer. Robotic surgery is associated with significantly lower EBL than both laparoscopy and laparotomy; fewer conversions but more complications than laparoscopy; and shorter LOHS, fewer complications, and fewer transfusions but a longer OT than laparotomy.

Limitations of Robotic Surgery

Apart from the absence of level 1 evidence regarding robotic-assisted laparoscopy for endometrial cancer, there are other limitations of robotic-assisted surgery to consider. These limitations can be categorized as physical limitations of the da Vinci System and cost considerations.

The limitations of robotic technology include: [21]

- Additional surgical training
- Increased costs and operating room time
- Bulkiness of the devices
- Instrumentation limitations (e.g., lack of a robotic suction and irrigation device, size, cost)

- Lack of haptics (tactile feedback)
- Risk of mechanical failure
- Limited number of energy sources (i.e., less than with conventional laparoscopy)
- Not designed for abdominal surgery involving more than two quadrants (the device needs to be re-docked and repositioned to operate in the quadrants it is not facing)

The development of the da Vinci Xi, with a longer reach and improved range, has in general enabled para-aortic lymph node dissection without much difficulty.

Robotic surgical systems are designed with features intended to minimize the potential effects of mechanical failures on patients [21]. Such features include system redundancy, so-called "graceful" performance degradation or failure, fault tolerance, just-in-time maintenance, and system alerting. In simplified terms, there are several mechanical checks and balances built into current robotic surgical systems so that the risk of mechanical failure is minimized.

Also as a result of the robotic arms being limited in its ability to reach away or in the cephalad direction, the placements of the ports are typically higher in a patient than compared to traditional laparoscopy in order to have access to both the pelvis and to the upper abdomen. These incisions, some of which are placed above the umbilicus, may be a cosmetic concern for some patients.

The absence of haptics or tactile feedback is also an important consideration in robotic-assisted surgery. Currently, there is no ability for the surgeon at the surgeon's console to receive tactile feedback regarding the "firmness of tissue" or the degree of tension one is exerting on tissue as would be the case in an open laparotomy or traditional laparoscopy procedure in which the surgeon is actually touching the tissue or holding instruments that are in direct contact with the patient; however, most surgeons would agree that as one gains more experience with the robot, the surgeon is able to use visual cues which enable a "virtual" tactile feel.

Another limitation of the robot already discussed has been in the bulkiness of the arms of the robot holding the robotic instruments. These have a greater propensity to clash if not positioned with adequate spacing in between, a situation that sometimes cannot be avoided in small, petite patients, but is seldom a problem for most endometrial cancer patients. Truncal obesity resulting in a greater abdominal surface area ironically results in an advantage, overcoming this limitation for many patients with endometrial cancers. The recent generation da Vinci Xi system which has a longer reach and thinner arms has improved many of the limitations discussed above.

Surgical Treatment in Stage III–IV Endometrial Cancer

Maximal surgical debulking is indicated in patients with a good performance status and resectable tumor [III, B]. For distant metastatic disease, palliative surgery could be considered in patients with a good performance status. When surgery is not

Table 7.1 Stage wise treatment protocol for endometrial cancer

Stage		Surgical treatment	Adjuvant treatment
I	IA G1–G2	Hysterectomy + BSO	
	IA G3	Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
	IB G1–G3	Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
II		Hysterectomy + BSO + bilateral pelvic and para-aortic lymphadenectomy	
III		Maximal surgical cytoreduction with good performance status	
IV	IVA	Anterior and posterior pelvic exenteration	
	IVB	Systemic therapy with palliative surgery	

feasible due to medical contraindications (5–10 % of patients), or because of irresectable disease, external radiotherapy with or without intracavitary brachytherapy to the uterus and vagina is suitable for individual clinical use [IV, B] (Table 7.1).

Adjuvant Treatment

Adjuvant treatment for endometrial cancer is offered based on surgical stage and adverse factors.

Radiotherapy

In 2009, a randomized trial compared vaginal brachytherapy vs. observation in stage IA G1–2 endometrial cancer with a similar overall recurrence rate, survival, and late toxic effect in the two groups. The optimal adjuvant treatment (Table 7.2) of intermediate-risk endometrial cancer is still to be defined. External beam radiation has been shown to reduce the rate of locoregional recurrence in intermediate-risk endometrial cancer. However, three large randomized studies (PORTEC-1 [13], GOG 99 [14], and ASTEC MRC-NCIC CTG EN.5 [15]) failed to demonstrate that radiation improves overall or disease-specific survival. A randomized clinical trial (PORTEC-2) comparing vaginal brachytherapy and external beam radiation in intermediate-risk patients showed that the two radiation therapies were equally effective but that the quality of life was better in the vaginal brachytherapy arm [16].

Chemotherapy

Platinum-based chemotherapy can be considered in stage I G3 with adverse risk factors (patient age, lymphovascular space invasion, and high tumor volume) and in

Table 7.2 Risk stratification and adjuvant Rx

Risk Category	Extent of disease	Adjuvant treatment
Low Risk	Superficial invasion (<1/2)	No further Rx
	Low grade (1/2)	
Intermediate Risk	High Grade	Vaginal Brachytherapy
	Deep Invasion	
	LVSI	
	Negative Lymph Nodes	
High Risk	Positive Lymph Nodes	External pelvic irradiation and vaginal brachytherapy – /+CT CT + Extended field RT
	Stage II	
	UPSC, CCCa	
	Positive P- A LNs	
PORTEC II Trial		

patients with stage II–III endometrial cancer [II, B]. Maggi et al. conducted a randomized trial in 345 high-risk patients comparing five courses of cisplatin, doxorubicin, and cyclophosphamide with external pelvic radiation. The authors reported no difference between therapies in terms of PFS or overall survival [17], a result which is also related to the insufficient sample size. A Japanese multicenter randomized trial compared whole-pelvic irradiation with three or more courses of cyclophosphamide, doxorubicin, and cisplatin chemotherapy in patients with old stage IC–IIIC endometrioid adenocarcinoma. No difference in overall survival, relapse rate, or PFS was observed [18]. In a subgroup analysis, chemotherapy appeared superior to pelvic radiotherapy in patients aged >70 years with outer half myometrial invasion, those with grade 3, those with stage II, or those with stage I disease and positive peritoneal cytology.

Combined Radiotherapy and Chemotherapy

Two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) were undertaken to clarify whether the sequential use of chemotherapy and radiotherapy improved PFS over radiotherapy alone in high-risk endometrial cancer patients (stage I–IIA, IIIC, any histology). The results of the two studies were pooled for analysis [19]. The combined modality treatment was associated with 36 % reduction in the risk of relapse or death [hazard ratio (HR) 0.64, 95 % confidence interval (CI) 0.41–0.99; $P = 0.04$]. Cancer-specific survival was significantly different (HR 0.55, 95 % CI 0.35–0.88; $P = 0.01$) and favored the use of adjuvant chemotherapy in addition to radiotherapy. The ongoing PORTEC-3 study is comparing radiotherapy with the concomitant and sequential use of chemotherapy and radiotherapy in patients with endometrioid stage I G3, stage II–III, and any stage serous and clear-cell carcinomas. Current evidence does not support the use of progestins in the adjuvant treatment of endometrial cancer [I, A].

Locoregional Recurrence

The standard treatment of vaginal recurrence in women who have not taken prior RT is radiotherapy (external beam plus vaginal brachytherapy) with high rates of local control, complete response (CR), and a 5-year survival of 50 %. For central pelvic recurrence, the treatment of choice is surgery or radiotherapy (no prior RT), while for regional pelvic recurrences, it is radiotherapy (no prior RT), associated with chemotherapy/hormone therapy.

Advanced Disease

There is no agreement on the standard treatment of women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy, and/or chemotherapy is employed.

In the GOG-122 trial, there were 396 patients with stage III and optimally debulked stage IV disease who were randomized to whole abdominal radiation or to doxorubicin-cisplatin chemotherapy; there was a significant improvement in both PFS (50 % vs. 38 %; $P = 0.07$) and overall survival (55 % vs. 42%; $P = 0.004$) in favor of chemotherapy [20].

Treatment of Metastatic Disease and Relapse

Systemic treatment of metastatic and relapsed disease may consist of endocrine therapy or cytotoxic chemotherapy. Hormonal therapy is recommended for endometrioid histologies only and involves mainly the use of progestational agents; tamoxifen and aromatase inhibitors are also used. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases. The overall response to progestins is ~25 %. Single cytotoxic agents have been reported to achieve a response rate up to 40 % in chemotherapy-naïve patients with metastatic endometrial cancer. Among those, platinum compounds, anthracyclines, and taxanes are most commonly used alone and in combination [21]. In nonrandomized trials, paclitaxel with carboplatin or cisplatin demonstrated a response rate of >60 % and a possibly prolonged survival compared with historical experience with other non-paclitaxel-containing regimens. Based upon these results, many consider that paclitaxel-based combination regimens are preferred for first-line chemotherapy of advanced and recurrent endometrial cancer. The GOG has completed accrual to a non-inferiority randomized phase III study evaluating carboplatin/paclitaxel vs. cisplatin/doxorubicin/paclitaxel in patients with stage III, IV, or recurrent endometrial cancer (GOG 209), and published results should be available soon. Preliminary results showed that the two-drug regimen was as good as the three-drug regimen in terms of activity against the cancer and overall survival, whereas it was less toxic. Endometrial cancer recurring after first-line chemotherapy is largely a chemoresistant disease. Various agents have been tested in a number

of small phase II trials in patients previously exposed to chemotherapy. Only paclitaxel has consistently shown a response rate of >20 %. Preliminary data for several molecularly targeted agents for endometrial cancer are emerging. The PI3K/Akt/mTOR pathway is frequently upregulated in women with endometrial cancer because of loss of the tumor suppressor gene PTEN. Inhibitors of the mammalian target of rapamycin (mTOR) have shown promising early results. The mTOR inhibitor temsirolimus was associated with a 24 % response rate in chemotherapy-naïve patients. In patients with previous treatment, a 4 % response rate with disease stabilization in 46 % has been reported [22]. A recent phase II clinical trial demonstrates that single-agent ridaforolimus has antitumor activity in women with advanced endometrial cancer, most of whom had received two prior chemotherapy regimens [23]. The study met its primary end point, as 29 % of patients achieved a clinical benefit, defined as an objective response or prolonged stable disease of 16 weeks or more. Ridaforolimus also showed an acceptable toxic effect profile. Unfortunately, predictive factors have not yet been identified to select patients most likely to benefit from mTOR inhibitor therapy.

Serous Carcinoma and Clear-Cell Carcinoma

Serous and clear-cell carcinoma requires complete staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, appendectomy, and peritoneal biopsies. They are more aggressive with higher rates of metastatic disease and lower 5-year survival rates [I, A]. There is considerable evidence from retrospective series that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves PFS and overall survival [III, B] [24]. Platinum-based chemotherapy is recommended in patients with stage III or IV [I, A]. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent serous or clear-cell uterine cancer. Historically serous endometrial cancers have not been considered to be hormone responsive.

Prognosis

Endometrial cancer is generally associated with a favorable prognosis. In the EUROCARE-4 study, age-adjusted 5-year relative survival estimates reached 76 % in 1995–1999 and 78 % in 2000–2002 in Europe. Survival for patients treated in 2000–2002 was highest generally in Northern Europe (especially in Sweden) and lowest in Eastern Europe (Czech Republic and Poland) [25]. A key factor leading to this good prognosis is that most cases are diagnosed at an early stage. The most important prognostic factors at diagnosis are stage, grade, depth of invasive disease, LVSI, and histological subtype. Endometrial tumors have a 5-year survival of 83 % compared with 62 % for clear-cell and 53 % for papillary carcinomas. LVSI is present in 25 % of cases. Five-year overall survival is 64 and 88 % with or without LVSI, respectively.

Given the importance of tumor stage for both prognosis and adjuvant treatment, it is necessary to compare the performance of the 1988 and 2009 FIGO staging systems. Based on the 2009 system, survival was 89.6 and 77.6 % for stage IA and IB. The newly defined stage IIIC substages are prognostically different. Survival for stage IIIC1 was 57 % compared with 49 % for stage IIIC2 [26]. The first Indian prospective randomized trail comparing open and robotic assisted surgery in endometrial cancers revealed that minimally invasive method is similar to open method with respect to oncological outcomes. It has the additional benefit of decreased blood loss, shorter duration of hospital stay and less postoperative complications [27].

Follow-Up and Long-Term Implications

Most recurrences will occur within the first 3 years after treatment. The suggested frequency of follow-up is every 3–4 months with physical and gynecological examination for the first 2 years and then with a 6-month interval until 5 years. Further investigations can be carried out if clinically indicated. PET/CT has been shown to be more sensitive and specific than CT alone for the assessment of suspected recurrent endometrial cancer. The utility of Pap smears for the detection of local recurrences has not been demonstrated.

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