

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

Endometrial cancer is cancer of the lining of the womb (uterus), known as the endometrium. The most common symptom is abnormal bleeding from the vagina. Surgery for endometrial cancer usually involves the removal of the uterus (hysterectomy). A laparoscopic hysterectomy is carried out through several small incisions in the abdomen ('keyhole' surgery), with the aid of an internal telescope and camera system (laparoscope).

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2010.

Procedure name

- Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer.

Specialty societies

- Royal College of Obstetricians and Gynaecologists
- British Society of Gynaecological Endoscopy.

Description

Indications and current treatment

Endometrial cancer

Endometrial cancer is the most common type of uterine cancer. In 2006, there were 7045 new cases of uterine cancer diagnosed in the UK and the age-standardised (European) annual incidence rate was 18.1 per 100,000 females. Uterine cancer is the fourth most common cancer in women in the UK and most cases are diagnosed in women older than 50 years (source: Cancer Research UK).

The most common symptom of endometrial cancer is abnormal vaginal bleeding, especially in postmenopausal women. The main treatment is surgery, which usually involves a total hysterectomy with bilateral salpingo-oophorectomy. Radiotherapy, hormone therapy and chemotherapy are also used, depending on the type, stage and grade of cancer. The stage is defined by the International Federation of Gynaecology and Obstetrics (FIGO) system: In stage I, the cancer is confined to the uterus; in stage II the cancer has spread to the cervix; in stage III the disease is more advanced but still confined to the true pelvis; in stage IV, the cancer has spread to another body organ. The cancer is graded according to how differentiated the cells are; from low-grade (G1), in which cells are well differentiated, to undifferentiated cells of high-grade (G3) cancer.

The suggested benefits of the laparoscopic approach to hysterectomy are smaller incisions and scars, shorter hospital stay and shorter recovery period than open surgery.

What the procedure involves

Laparoscopic hysterectomy is usually performed under general anaesthesia. The abdomen is first insufflated with carbon dioxide, and a number of small incisions are made to provide access for the laparoscope and surgical instruments. A uterine manipulator is attached to the uterine cervix and extended into the body of the uterus. This is used to move the uterus in different directions to aid the surgical procedure. A hysterectomy is performed by initially dividing the round ligaments and the broad ligaments. If the ovaries are to be left in position, the utero-ovarian ligaments are transected, and the ovarian pedicles are left intact. The uterine vessels are divided laparoscopically in a total laparoscopic hysterectomy or vaginally in a laparoscopically assisted vaginal hysterectomy. The ureters are dissected carefully to the point of their insertion into the bladder. The uterosacral ligaments are then divided, thus releasing the uterus and cervix, which are removed intact through the vagina. Sometimes, the pelvic lymph nodes and para-aortic lymph nodes are also removed through one of the abdominal incisions or through the vagina.

IP overview: Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer. Searches were conducted of the following databases, covering the period from their commencement to 3 February 2010: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with endometrial cancer.
Intervention/test	Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy).
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on a meta-analysis of 5 RCTs including 498 patients, 1 additional RCT including 2616 patients, 3 non-randomised comparative studies including 988 patients and 1 case series including 7 patients¹⁻¹³.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on laparoscopic hysterectomy for endometrial cancer

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio																																							
Study details	Key efficacy findings	Key safety findings	Comments																																				
Palomba S (2009)^{1,2} Meta-analysis (RCTs) Search date: March 2009 Study population: Women with histologically confirmed endometrial cancer n = 498 (253 LH vs 245 AH) Study selection criteria: All RCTs evaluating the effects of laparoscopic approach to endometrial cancer. Five RCTs were identified and included in the final analysis: Malzoni et al. (2009)³ n = 159 (81 vs 78), stage I, follow-up = 38.5 months Tozzi et al. (2005)⁴ n = 122 (63 vs 59), stage I–III, follow-up = 44 months Zorlu et al. (2005)⁵ n = 52 (26 vs 26), stage I, follow-up ‘not clearly defined’ Zullo et al. (2009)⁶ n = 78 (40 vs 38), stage I, follow-up = 79 months Fram et al. (2002)⁷ n = 61 (29 vs 32), stage I, follow-up ‘not clearly defined’ Technique: surgical procedure consisted of total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, systematic inspection of peritoneal cavity with biopsy of each suspected lesion, and eventual pelvic and para-aortic lymphadenectomy. Conflict of interest/source of funding: none declared	Overall survival rate (3 RCTs, n = 359): - LH = 91.8% (169/184) - AH = 88.0% (154/175), p = 0.976 OR = 0.96 (95% CI 0.51 to 1.81) (test for heterogeneity, p = 0.824) Disease-free survival rate (3 RCTs, n = 359): - LH = 87.5% (161/184) - AH = 88.0% (154/175), p = 0.986 OR = 0.95 (95% CI 0.51 to 1.80) (test for heterogeneity, p = 0.674) Cancer-related survival rate (3 RCTs, n = 359): - LH = 39.1% (9/23) - AH = 42.9% (9/21), p = 0.883 OR = 0.91 (95% CI 0.27 to 3.06) (test for heterogeneity, p = 0.542) Mean operative time (min): <table><tr><th>Study</th><th>LH</th><th>AH</th></tr><tr><td>Fram et al.</td><td>136.2</td><td>101.9</td></tr><tr><td>Zullo et al.</td><td>196.7</td><td>135.3</td></tr></table> OR = 53.5 (95% CI 37.3 to 69.7) (test for heterogeneity, p = 0.136) Mean blood loss (ml): <table><tr><th>Study</th><th>LH</th><th>AH</th></tr><tr><td>Fram et al.</td><td>145.5</td><td>501.6</td></tr><tr><td>Tozzi et al.</td><td>241.3</td><td>586.1</td></tr><tr><td>Zullo et al.</td><td>173.9</td><td>282.5</td></tr></table> OR = -266.86 (95% CI -454.8 to -78.9) (test for heterogeneity, p = 0.005) Mean pelvic nodes yield: <table><tr><th>Study</th><th>LH</th><th>AH</th></tr><tr><td>Fram et al.</td><td>21.3</td><td>21.9</td></tr><tr><td>Zorlu et al.</td><td>18.2</td><td>21.1</td></tr><tr><td>Tozzi et al.</td><td>19.3</td><td>18.2</td></tr><tr><td>Zullo et al.</td><td>11.5</td><td>10.7</td></tr></table> OR = 0.62 (95% CI -1.47 to 2.71) (test for heterogeneity, p = 0.56)	Study	LH	AH	Fram et al.	136.2	101.9	Zullo et al.	196.7	135.3	Study	LH	AH	Fram et al.	145.5	501.6	Tozzi et al.	241.3	586.1	Zullo et al.	173.9	282.5	Study	LH	AH	Fram et al.	21.3	21.9	Zorlu et al.	18.2	21.1	Tozzi et al.	19.3	18.2	Zullo et al.	11.5	10.7	Intraoperative complications (not further defined) - LH = 8.3% (14/169) - AH = 11.7% (19/162), p = 0.390 OR = 1.60 (95% CI 0.49 to 5.22) (test for heterogeneity, p = 0.256) Postoperative complications (not further defined) - LH = 17.1% (27/158) - AH = 32.3% (50/155), p = 0.007 OR = 0.40 (95% CI 0.23 to 0.70) (test for heterogeneity, p = 0.467)	Study design issues: - An update to the meta-analysis was published after the main paper, including an additional study in the survival analysis. The updated results have been presented here. - Primary end-point was overall survival assessed at 6, 12, 24 and 36-month follow-up. - Secondary end-points were disease-free survival, cancer-related survival, quality of life (not reported), operative time, blood loss, nodes yield, complication rate and costs. - Only 3 RCTs reported the primary outcome. - The outcome measures were defined as dichotomous data or weighted mean difference. The analysis of treatment effect was performed on intention-to-treat basis, considering dropouts and missing data as treatment failures, and per-protocol basis considering the results from evaluated patients alone. Other issues: - The individual totals listed for the intraoperative complications do not add up to the overall total in the paper.
Study	LH	AH																																					
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Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
Malzoni M (2009)³ Randomised controlled trial Italy Study period: 2001–2006 Study population: women with early stage endometrial cancer n = 159 (81 LH, 78 AH) Mean age (years): LH = 60; AH = 63 Inclusion criteria: clinical stage I endometrial cancer. Exclusion criteria included ovarian lesions, obvious metastasis beyond the uterus, abnormal Papanicolaou smear, bulky uterus ≥ 12 week size or where vaginal removal of the uterus may require morcellation, BMI 40 or above, age 80 years or older. Technique: total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy. Para-aortic lymphadenectomy was done when positive lymph nodes were discovered. The fallopian tubes were routinely coagulated to minimise the risk of tumour spread during manipulation of the uterus. 62% (98/159) patients received adjuvant treatment. Median follow-up: 38.5 months (range 2–81) Conflict of interest/source of funding: none declared	Number of patients analysed: 159 (81 vs 78) Recurrence rate: - LH = 8.6% (7/81) - AH = 11.5% (9/78), p = NS Local recurrence: - LH = 3.7% (3/81) - AH = 5.1% (4/78) Distant recurrence: - LH = 4.9% (4/81) - AH = 6.4% (5/78) Overall survival rates (projected by Kaplan-Meier curves): - LH = 93.2% - AH = 91.1%, p = 0.31 Disease-free survival rates: - LH = 91.4% - AH = 88.5%, p = 0.28 Mean number of pelvic lymph nodes resected: - LH = 23.5 $\pm$ 5.8 - AH = 22.2 $\pm$ 5.4, p = NS Mean operative time (min): - LH = 136 $\pm$ 31 - AH = 123 $\pm$ 29, p < 0.01 Mean blood loss (ml): - LH = 50 $\pm$ 12 - AH = 145 $\pm$ 35, p < 0.01 Mean length of hospital stay (days): - LH = 2.1 $\pm$ 0.5 - AH = 5.1 $\pm$ 1.2, p < 0.01	There were no conversions to open surgery. Bladder injury: - LH = 1.2% (1/81) - AH = 2.6% (2/78) Postoperative haematoma: - LH = 1.2% (1/81) - AH = 0% (0/78) Dehiscence in first month after surgery: - LH = 2.5% (2/81) - AH = 0% (0/78) Postoperative fever: - LH = 8.6% (7/81) - AH = 11.5% (9/78) Lymphorrhoea (profuse discharge of lymphatic fluid from vaginal cuff): - LH = 23.4% (19/81) - AH = 21.8% (17/78)	This study was included in the meta-analysis Study design issues: - Prospective study with consecutive patients. - Randomisation was performed using a computer-generated randomisation list drawn up by a statistician. Study population issues: - There were no significant differences between the groups with regard to mean age, weight, BMI, histology type, grading, tumour stage and lymph node status. - There were no significant differences between the groups with regard to adjuvant treatment.

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
Tozzi R (2005)⁴ Randomised controlled trial Germany Study period: 1995–2002 Study population: women with endometrial cancer n = 122 (63 LH, 59 AH) Mean age (years): - LH = 67 - AH = 66 Inclusion criteria: histologically confirmed cancer of the corpus uteri. Exclusion criteria: uterine size exceeding transversal diameter of 8 cm by sonography, precluding vaginal removal. Technique: Laparoscopic assisted vaginal hysterectomy with bilateral salpingo-oophorectomy plus bilateral pelvic and para-aortic lymphadenectomy in patients with FIGO stage greater than I. No uterine manipulator was used and closure of the fallopian tubes was always the first step. If histology showed cervical involvement, a type II radical hysterectomy was performed. Patients with FIGO stage III or IV disease were treated with debulking surgery by laparotomy. 64% (78/122) of patients received adjuvant treatment. Median follow-up: 44 months (range 5–96) Conflict of interest: not reported	Number of patients analysed: 122 (63 vs 59) Recurrence rate: - LH = 12.6% (8/63) - AH = 8.5% (5/59) Local recurrence: - LH = 3.2% (2/63) - AH = 1.7% (1/59) Distant recurrence: - LH = 9.5% (6/63) - AH = 6.8% (4/59) Overall survival rates (projected by Kaplan-Meier curves): - LH = 82.7% - AH = 86.5%, p = 0.33 Disease-free survival rates: - LH = 87.4% - AH = 91.6%, p = 0.38 Cause specific survival rates: - LH = 90.5% - AH = 94.9%, p = 0.47 Mean number of pelvic lymph nodes resected: - LH = 19.3 - AH = 18.2 Mean blood loss (ml): - LH = 241.3 - AH = 586.1, p = 0.02 Mean length of hospital stay (days): - LH = 7.8 - AH = 11.4, p = 0.001 Return of bowel activity (days): - LH = 2.0 - AH = 2.3, p = 0.02	Conversions to open surgery = 8% (5/63) (4 conversions were due to the presence of intraperitoneal disease and 1 was due to a small bowel lesion during adhesiolysis) The authors state that one major complication occurred in each group but do not specify further. ‘Long-term complications’ (not further specified): - LH = 12% - AH = 34%, p = 0.02	This study was included in the meta-analysis. Study design issues: - Prospective study with consecutive patients. - Randomisation was performed by using a centrally managed random number table. - Intention to treat analysis. Study population issues: - There were no significant differences between the groups with regard to age, concurrent morbidity, parity, Quetelet index (BMI), previous surgery and history of malignant disease. Histologic type, grade and stage distribution was similar in the two groups. - There were no significant differences between the groups with regard to adjuvant treatment.

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
	<i>Patients with FIGO stage I disease (n = 93, 45 vs 48)</i> Recurrence rate: • LH = 8.8% (4/45) • AH = 6.2% (3/48) Local recurrence: • LH = 2.2% (1/45) • AH = 2.1% (1/48) Distant recurrence: • LH = 6.7% (3/45) • AH = 4.2% (2/48) Overall survival rates (projected by Kaplan-Meier curves): • LH = 86.5% • AH = 89.7%, p = 0.29 Disease-free survival rates: • LH = 91.2% • AH = 93.8%, p = 0.27 Cause specific survival rates: • LH = 93.4% • AH = 95.9%, p = 0.34		

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
Zullo F (2009)⁸ Randomised controlled trial Italy Study period: 2001–2003 Study population: women with early stage endometrial cancer n = 84 (42 LH, 42 AH) Mean age (years): not reported Inclusion criteria: not listed Technique: not described Median follow-up: 79 months (range 19–84) Conflict of interest/source of funding : none declared	Number of patients analysed: 78 (40 vs 38) Recurrence rate: - LH = 20.0% (8/40) - AH = 18.4% (7/38), p = 0.86 37.5% (3/8) of the recurrences in the LH group and 28.6% (2/7) of the recurrences in the AH group were detected at follow-up visits. The other patients with recurrence were symptomatic. Vaginal cuff recurrence: - LH = 7.5% (3/40) - AH = 0% (0/38), p = 0.09 Port site recurrence: - LH = 2.5% (1/40) - AH = 0% (0/38), p = 0.33 Pelvic recurrence: - LH = 5.0% (2/40) - AH = 10.5% (4/38), p = 0.36 Distant metastases: - LH = 5.0% (2/40) - AH = 2.6% (1/38), p = 0.59 Mortality at end of follow-up: - LH = 17.5% (7/40) - AH = 15.8% (6/38), p = 0.84 Disease-specific mortality at end of follow-up: - LH = 15.0% (6/40) - AH = 13.2% (5/38), p = 0.82 Overall survival rates after median follow-up of 44 months (Kaplan-Meier analysis): - LH = 82.7% - AH = 86.5%, p = 0.33 Disease-free survival rates after median follow-up of 44 months (Kaplan-Meier analysis): - LH = 87.4% - AH = 91.6%, p = 0.38	No safety outcomes were reported.	An earlier report from the same study centre was included in the meta-analysis Follow-up issues: 6 women (2 in the LH group and 4 in the AH group) were excluded from the analysis because they missed the first follow-up visit. Study design issues: - Patients were assigned randomly to 2 treatment groups with the use of a computer-generated list.

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
	Quality of life During the first 3 years after surgery, the total Italian version of the Short-Form Healthy Survey (SF-36) score was significantly higher in the laparoscopic group than the laparotomy group ($p < 0.05$). At the 4-year follow-up visit and thereafter, there was no significant difference between the groups.		

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
Walker JL (2009)⁹ Randomised controlled trial USA Study period: 1996–2005 Study population: women with FIGO clinical stage I to IIA uterine cancer n = 2616 (1696 LH, 920 AH) Median age = 63 years Inclusion criteria: clinical stage I to IIA uterine cancer, adequate bone marrow and renal and hepatic function, Gynecologic Oncology Group performance status < 4. Technique: Laparoscopic hysterectomy included laparoscopic-assisted techniques, total laparoscopic approaches and rarely, robotics. Surgeons varied as to whether they completed the lymph node dissection once a positive lymph node was documented. Median follow-up: not reported Conflict of interest/source of funding: none	Number of patients analysed: 2591 (1682 vs 909) Failure to successfully complete laparoscopy was greater with increasing age (OR = 1.27, 95% CI 1.14 to 1.42 for a 10-year increase in age), increasing BMI (OR = 1.11, 95% CI 1.09 to 1.13 for a one-unit increase in BMI), and metastatic disease (OR = 2.54, 95% CI 1.90 to 3.41). Median operative time (min): - LH = 204 - AH = 130, p < 0.001 Median length of hospital stay (days): - LH = 3 - AH = 4, p = not reported Proportion of patients requiring more than 2 days in hospital after surgery : - LH = 52% - AH = 94%, p < 0.0001 Median number of pelvic lymph nodes resected: - LH = 17 - AH = 18, p = not reported Proportion of patients without pelvic and para-aortic node removal: - LH = 8% - AH = 4%, p < 0.0001 No difference in overall detection of advanced stage (IIIA and above) was seen.	Conversions to open surgery = 25.8% (434/1682) Reasons for conversion: - Poor exposure, n = 246 - Cancer requiring laparotomy for resection, n = 69 - Excessive bleeding, n = 49 - Other causes, n = 70 30-day mortality: - LH = 0.6% (10/1682) - AH = 0.9% (8/909), p = 0.404 (10 pulmonary embolus, 3 complications requiring reoperation, 1 haemorrhage, 2 progressive stage IVB cancer and chemotherapy, 2 infection/sepsis) Intraoperative complications Total: - LH = 9.5% (160/1682) - AH = 7.6% (69/909), p = 0.106 Bowel injury: - LH = 2.2% (37/1682) - AH = 1.8% (16/909) Vein injury: - LH = 2.7% (45/1682) - AH = 2.5% (23/909) Artery injury: - LH = 1.8% (30/1682) - AH = 0.7% (6/909) Bladder injury: - LH = 1.2% (21/1682) - AH = 0.8% (7/909) Ureter injury: - LH = 0.8% (14/1682) - AH = 0.7% (6/909)	Study design issues: - Random assignment was conducted by a permuted block design with approximately twice as many patients undergoing laparoscopy compared with laparotomy. - The primary outcome of the study was recurrence-free survival but these data have not yet been reported. - Intent to treat analysis. Study population issues: 25 patients (14 assigned to LH and 11 assigned to AH did not have surgery). Reasons included refusal of randomised treatment, comorbidities, insurance issues, and patient moved or went to a different centre. - The two groups were similar with regard to surgical stage and type of cancer (the majority of tumours were endometrioid adenocarcinoma).

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
		Postoperative complications (classified as grade 2 or above on the National Cancer Institute Common Toxicity Criteria) Total: - LH = 14.3% (240/1682) - AH = 21.0% (191/909), $p < 0.001$ Urinary tract infection: - LH = 2.1% (35/1682) - AH = 3.0% (27/909) Pelvic cellulitis: - LH = 0.8% (14/1682) - AH = 0.9% (8/909) Abscess: - LH = 1.0% (17/1682) - AH = 0.7% (6/909) Bowel obstruction: - LH = 0.8% (14/1682) - AH = 1.3% (12/909) Ileus: - LH = 3.9% (66/1682) - AH = 7.5% (68/909), $p < 0.005$ Wound infection: - LH = 3.2% (53/1682) - AH = 3.6% (33/909) Urinary fistula: - LH = 0.4% (6/1682) - AH = 0.1% (1/909) Bowel fistula: - LH = 0.4% (6/1682) - AH = 0.2% (2/909) Arrhythmia: - LH = 0.9% (15/1682) - AH = 2.4% (22/909), $p < 0.005$	

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio																																				
Study details	Key efficacy findings	Key safety findings	Comments																																	
Cho Y-H (2007)¹⁰ Non-randomised comparative study Korea Recruitment period: 1997–2006 Study population: women with clinical stage I or II endometrial carcinoma n = 309 (165 LH, 144 AH) Mean age (years): - LH = 50.0 (range 26–77) - AH = 51.9 (range 31–77) Patient selection criteria: patients with clinical stage I or II uterine cancer diagnosed by pelvic examination and imaging. After histopathological staging, patients with uterine sarcoma were excluded. Technique: Laparoscopic surgery included laparoscopically assisted vaginal hysterectomy and pelvic and/or para-aortic lymph node dissection. Open surgery included total abdominal hysterectomy. Median follow-up (months): - LH = 28 - AH = 51, p < 0.001 Conflict of interest/source of funding: not reported	Number of patients analysed: 309 (165 vs 144). Recurrence: - LH = 3.0% (5/165) - AH = 3.5% (5/144), p = 1.00 4 patients in the LH group had vaginal cuff recurrence, 3 accompanied by distant metastases. All 5 patients in the AH group had distant metastases. The median time to relapse was 16 months in LH group and 25 months in AH group (p = 0.21). Tumour-related deaths: - LH = 0.6% (1/165) - AH = 1.4% (2/144), p = 0.60 5-year progression-free survival rates: - LH = 95.5% - AH = 96.5%, p = 0.74 5-year overall survival rates: - LH = 98.0% - AH = 98.1%, p = 0.82 <i>Operative outcomes</i> Pelvic lymphadenectomy: - LH = 89.7% (148/165) - AH = 89.6% (129/144), p = 1.00 Para-aortic lymphadenectomy: - LH = 17.6% (29/165) - AH = 28.5% (41/144), p = 0.03 Mean number of pelvic nodes (range): - LH = 26.2 (1–70) - AH = 25.5 (7–65), p = 0.61 Operative time (min): - LH = 154.9 (55–478) - AH = 166.2 (75–360), p = 0.08 Hospital stay (days): - LH = 9.5 (3–38) - AH = 14.3 (5–85), p < 0.001	Conversions to laparotomy = 5.3% (10/188) (7 conversions were due to intraperitoneal adhesions and 3 were due to inadequate ventilation or uncontrollable high blood pressure. One of these 3 patients had a BMI of 37 kg/m² and the others had BMIs of between 25 and 30 kg/m². Intraoperative complications for LH: - Great vessel injury = 1.2% (2/165) - Bladder injury = 1.2% (2/165) - Ureter injury = 0.6% (1/165) - Bowel injury = 0.6% (1/165) There were no intraoperative complications for AH. Postoperative complications: <table><tr><th></th><th>LH</th><th>AH</th></tr><tr><td>Wound infection/dehiscence</td><td>0.6% (1/165)</td><td>5.6% (8/144)</td></tr><tr><td>Lymphocyst</td><td>1.2% (2/165)</td><td>4.2% (6/144)</td></tr><tr><td>Intra-abdominal abscess</td><td>2.4% (4/165)</td><td>5.6% (8/144)</td></tr><tr><td>Ileus</td><td>0</td><td>2.1% (3/144)</td></tr><tr><td>Deep vein thrombosis</td><td>0</td><td>1.4% (2/144)</td></tr><tr><td>Pulmonary embolism</td><td>0</td><td>0.7% (1/144)</td></tr><tr><td>Incisional hernia</td><td>0.6% (1/165)</td><td>0</td></tr><tr><td>Obturator neuropathy</td><td>0.6% (1/165)</td><td>0</td></tr><tr><td>Bladder dysfunction</td><td>0.6% (1/165)</td><td>0.7% (1/144)</td></tr><tr><td>Vesico-vaginal fistula</td><td>0</td><td>0.7% (1/144)</td></tr></table>		LH	AH	Wound infection/dehiscence	0.6% (1/165)	5.6% (8/144)	Lymphocyst	1.2% (2/165)	4.2% (6/144)	Intra-abdominal abscess	2.4% (4/165)	5.6% (8/144)	Ileus	0	2.1% (3/144)	Deep vein thrombosis	0	1.4% (2/144)	Pulmonary embolism	0	0.7% (1/144)	Incisional hernia	0.6% (1/165)	0	Obturator neuropathy	0.6% (1/165)	0	Bladder dysfunction	0.6% (1/165)	0.7% (1/144)	Vesico-vaginal fistula	0	0.7% (1/144)	Study design issues: - Retrospective - A total of 349 (188 vs 161) patients were initially treated. Ten patients who underwent laparoscopy but were converted to laparotomy were excluded from the analysis. An additional 30 patients were excluded from the analysis after histopathological results led to upstaging. Study population issues: - Patients in the AH group had significantly longer follow-up than those in the LH group. - The two groups did not differ significantly in age, parity, BMI, surgical stage, histological type, grade and tumour size. - Postoperative adjuvant therapy was administered to 22% (36/165) of patients in the LH group and 30% (43/144) of patients in the AH group (p = 0.118).
	LH	AH																																		
Wound infection/dehiscence	0.6% (1/165)	5.6% (8/144)																																		
Lymphocyst	1.2% (2/165)	4.2% (6/144)																																		
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Incisional hernia	0.6% (1/165)	0																																		
Obturator neuropathy	0.6% (1/165)	0																																		
Bladder dysfunction	0.6% (1/165)	0.7% (1/144)																																		
Vesico-vaginal fistula	0	0.7% (1/144)																																		

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
		p = 0.002 (for all complications)	

Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio																																							
Study details	Key efficacy findings	Key safety findings	Comments																																				
Obermair A (2004)¹¹ Non-randomised comparative study Australia Recruitment period: 1993–2001 Study population: women with endometrial carcinoma n = 510 (226 LH, 248 AH) Mean age (years): - LH = 61.7 - AH = 64.5, p = 0.008 Exclusion criteria: patients with previous or concurrent malignancy. Patients with uterine size larger than 10 weeks or evidence of extrauterine disease were not considered eligible for LH. Technique: Laparoscopic surgery included total laparoscopic hysterectomy. Depending on the intraoperative assessment by frozen section examination, a surgical staging, which included peritoneal washings and pelvic/aortic lymphadenectomy was performed or omitted. Median follow-up = 29 months Conflict of interest/source of funding: not reported	Number of patients analysed: 510 (226 vs 248). Recurrence: - LH = 4.0% (9/226) - AH = 14.9% (37/248), p = not reported Sites of recurrence were: vaginal vault = 10, pelvis = 7, abdomen = 9, distant = 18, multiple = 2 Overall survival for all patients at 60 months = 77.5% Multivariate Cox models on disease-free survival <table><tr><td></td><td>OR</td><td>95% CI</td></tr><tr><td>LH vs AH</td><td>1.3</td><td>0.5 to 2.9</td></tr><tr><td>Age (continuous)</td><td>1.06</td><td>1.02 to 1.09</td></tr><tr><td>Stage (I vs II vs III vs IV)</td><td>2.4</td><td>1.7 to 3.6</td></tr><tr><td>Grade (1 vs 2 vs 3)</td><td>1.5</td><td>0.9 to 2.5</td></tr><tr><td>Lymph node dissection</td><td>2.2</td><td>0.9 to 5.0</td></tr></table> Multivariate Cox models on overall survival <table><tr><td></td><td>OR</td><td>95% CI</td></tr><tr><td>LH vs AH</td><td>0.7</td><td>0.4 to 1.3</td></tr><tr><td>Age (continuous)</td><td>1.05</td><td>1.03 to 1.08</td></tr><tr><td>Stage (I vs II vs III vs IV)</td><td>2.4</td><td>1.7 to 3.2</td></tr><tr><td>Grade (1 vs 2 vs 3)</td><td>1.6</td><td>1.1 to 2.5</td></tr><tr><td>Lymph node dissection</td><td>1.2</td><td>0.7 to 2.3</td></tr></table> No port-site recurrence was detected in the laparoscopy group.		OR	95% CI	LH vs AH	1.3	0.5 to 2.9	Age (continuous)	1.06	1.02 to 1.09	Stage (I vs II vs III vs IV)	2.4	1.7 to 3.6	Grade (1 vs 2 vs 3)	1.5	0.9 to 2.5	Lymph node dissection	2.2	0.9 to 5.0		OR	95% CI	LH vs AH	0.7	0.4 to 1.3	Age (continuous)	1.05	1.03 to 1.08	Stage (I vs II vs III vs IV)	2.4	1.7 to 3.2	Grade (1 vs 2 vs 3)	1.6	1.1 to 2.5	Lymph node dissection	1.2	0.7 to 2.3	Conversions to laparotomy = 4.9% (11/226) (6 conversions were due to intraperitoneal adhesions and 5 were to control significant haemorrhage)	Follow-up issues: - At the time of analysis, 3.1% (16/510) patients were lost to follow-up. Study design issues: - Retrospective - Patients were allocated to LH or AH according to the surgeon's preference. - Intention to treat analysis. Study population issues: - The authors note that there is an over-representation of 'low-risk' tumours in the laparoscopic group. - Patients in LH group were significantly younger, heavier and had a higher ASA (American Society of Anaesthesiologists) score. - Patients in the LH group were more likely to present with stage IA or IB and with grade 1, endometrioid tumours confined to the inner half of the myometrium.
	OR	95% CI																																					
LH vs AH	1.3	0.5 to 2.9																																					
Age (continuous)	1.06	1.02 to 1.09																																					
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Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio																																							
Study details	Key efficacy findings	Key safety findings	Comments																																				
Kalogiannidis I (2007)¹² Non-randomised comparative study Belgium Recruitment period: 1995–2003 Study population: women with clinical stage I endometrial adenocarcinoma n = 169 (69 LH, 100 AH) Mean age (years): not reported Exclusion criteria for LH: poor uterine mobility, uterine diameter > 10 cm on ultrasonography, BMI > 35, previous pelvic or abdominal irradiation, severe cardiopulmonary disease. Technique: Laparoscopic surgery included laparoscopically assisted vaginal hysterectomy. Pelvic lymphadenectomy was performed only in the ‘high-risk’ group (not defined). Median follow-up = 51 months Conflict of interest/source of funding: not reported	Number of patients analysed: 169 (69 vs 100). Recurrence: - LH = 8.7% (6/69) (median time 26 months after primary treatment) - AH = 16% (16/100) (median time 10 months after primary treatment) No port-site recurrence was detected in the laparoscopy group. Actuarial overall survival: - LH = 93% - AH = 86% Actuarial disease-free survival: - LH = 91% - AH = 84% Multivariate analysis for disease-free survival <table><tr><th></th><th>OR</th><th>95% CI</th></tr><tr><td>LH vs AH</td><td>1.9</td><td>0.7 to 5.4</td></tr><tr><td>Stage (I vs II vs III vs IV)</td><td>0.7</td><td>0.3 to 2.0</td></tr><tr><td>Grade (1 vs 2 vs 3)</td><td>1.4</td><td>0.8 to 2.7</td></tr><tr><td>Lymph-adenectomy</td><td>0.6</td><td>0.1 to 1.8</td></tr><tr><td>Histology type*</td><td>3.6</td><td>1.3 to 10.0</td></tr></table> Multivariate analysis for overall survival <table><tr><th></th><th>OR</th><th>95% CI</th></tr><tr><td>LH vs AH</td><td>3.2</td><td>1.0 to 10.0</td></tr><tr><td>Stage (I vs II vs III vs IV)</td><td>0.52</td><td>0.15 to 1.8</td></tr><tr><td>Grade (1 vs 2 vs 3)</td><td>2.3</td><td>1.1 to 4.7</td></tr><tr><td>Lymphadenectomy</td><td>0.3</td><td>0.06 to 1.1</td></tr><tr><td>Histology type*</td><td>7.8</td><td>2.1 to 29.0</td></tr></table> * endometrioid vs non-endometrioid		OR	95% CI	LH vs AH	1.9	0.7 to 5.4	Stage (I vs II vs III vs IV)	0.7	0.3 to 2.0	Grade (1 vs 2 vs 3)	1.4	0.8 to 2.7	Lymph-adenectomy	0.6	0.1 to 1.8	Histology type*	3.6	1.3 to 10.0		OR	95% CI	LH vs AH	3.2	1.0 to 10.0	Stage (I vs II vs III vs IV)	0.52	0.15 to 1.8	Grade (1 vs 2 vs 3)	2.3	1.1 to 4.7	Lymphadenectomy	0.3	0.06 to 1.1	Histology type*	7.8	2.1 to 29.0	Conversions to laparotomy = 5.5% (4/73) (3 conversions were due to intraperitoneal adhesions and 1 was due to cervical infiltration) Complications (not further defined): - LH = 7% - AH = 8% Estimated blood loss was significantly greater in AH group.	Follow-up issues: - No losses to follow-up were described Study design issues: - Prospective - Consecutive patients Study population issues: - Patients undergoing LH were more likely to present with surgical stage IA disease than those undergoing AH. - The authors note that the AH group was characterised by less favourable pathologic variables.
	OR	95% CI																																					
LH vs AH	1.9	0.7 to 5.4																																					
Stage (I vs II vs III vs IV)	0.7	0.3 to 2.0																																					
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Abbreviations used: AH, abdominal hysterectomy; BMI, body mass index; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LH, laparoscopic hysterectomy; NS, not significant; OR, odds ratio			
Study details	Key efficacy findings	Key safety findings	Comments
Logani S (2008)¹³ Case series USA Study period: not stated Study population: women who underwent total laparoscopic hysterectomy with lymph node dissection for endometrial cancer or complex atypical hyperplasia n = 7 Median age = 60 years Inclusion criteria: none stated Technique: total laparoscopic hysterectomy with lymph node dissection. Mean follow-up = 19 months Conflict of interest: none stated	<i>Artifact of mechanical transportation of endometrial tumour tissue into vascular channels in hysterectomy specimens</i> Index case: a 67 year old patient underwent total LH for endometrial cancer. On gross examination, the uterine cavity contained a 2.5 cm tumour and extensive lymph vascular involvement by the tumour was noted. The extensive lymph vascular involvement was considered to be unusual and the possibility of an artifact was raised. Following this case, all LH specimens were reviewed for the presence or absence of tumour/non-neoplastic endometrial tissue in vascular spaces. Tumour within blood vessels was noted in 5 of 7 specimens. No adjuvant therapy was prescribed for any of these patients. At follow-up, all patients are well without recurrence. The authors note that this artifact does not appear to be associated with any adverse prognosis but it has the potential of being incorrectly reported as vascular invasion. The authors note that the closed pressure system created by their laparoscopic technique is likely to be responsible for the mechanical transportation of the endometrial tissue into vascular spaces.		Retrospective review of laparoscopic hysterectomy specimens. Six to 19 slides from each patient were reviewed.

Efficacy

Survival

In a meta-analysis of 3 randomised-controlled trials (RCTs) including 359 patients with 38, 44 and 79 months of follow-up respectively, there were no significant differences in survival between LH and AH^{1, 2}. The overall survival rate was 92% (169/184) for patients in the LH group and 88% (154/175) for patients in the AH group ($p = 0.976$). The disease-free survival rate was 88% (161/184) for LH and 88% (154/175) for AH ($p = 0.986$). The cancer-related survival rate was 39% (9/23) for patients in the LH group and 43% (9/21) for patients in the AH group ($p = 0.88$).

A non-randomised comparative study of 309 patients reported 5-year overall survival rates of 98% for both LH and AH¹⁰. The 5-year progression-free survival rate was 96% for patients after LH and 97% for patients after AH ($p = 0.74$).

Recurrence

Three RCTs with follow-up ranging from 38 to 79 months reported similar rates of recurrence for patients in the LH and AH groups^{3,4,8}. Rates of recurrence after LH were 9% (7/81), 13% (8/63) and 20% (8/40) compared with 12% (9/78), 8% (5/59) and 18% (7/38) respectively, after AH.

In one of these RCTs, including 40 patients treated by LH, there was a single case of port-site recurrence (2.5%) after a median follow-up of 79 months⁸.

Length of hospital stay

Three RCTs of 159, 122 and 2616 patients reported the length of hospital stay^{3,4,9}. In 2 studies, the hospital stay after LH was statistically significantly shorter than after AH (2 vs 5 days, $p < 0.01$; 8 vs 11 days, $p = 0.001$)^{3,4}. In the remaining study, the proportion of patients staying more than 2 days was significantly higher in the AH group (94% vs 52%, $p < 0.0001$)⁹.

Safety

Six studies reported rates of conversion to laparotomy to be 0% (0/81), 26% (434/1682), 5% (10/188), 5% (11/226), 5% (4/73), 8% (5/63),^{3,4,9,10,11,12}.

A RCT of 2616 patients reported similar rates of intraoperative complications for LH and AH (10% [160/1682] vs 8% [69/909], $p = 0.106$) but significantly fewer postoperative complications for LH compared with AH (14% [240/1682] vs 21% [191/909], $p < 0.001$)⁹.

A meta-analysis also reported that the rate of intraoperative complications was similar for both LH and AH (8% [14/169] vs 12% [19/162], $p = 0.39$)¹. There were,

however, significantly fewer postoperative complications associated with LH compared to AH (17% [27/158] vs 32% [50/155], $p = 0.007$).

In two studies including a total of 1847 patients undergoing LH, intraoperative complications included bowel injury (2% [37/1682] and <1% [1/165]), vascular injury (4% [75/1682] and 1% [2/165]), bladder injury (1% [21/1682] and 1% [2/165]) and ureter injury (<1% [14/1682] and <1% [1/165])^{9,10}. In the non-randomised comparative study of 309 patients treated by laparoscopic or abdominal hysterectomy, intra-abdominal abscess was reported in 2% (4/165) and 6% (8/144) of patients respectively⁹.

The RCT of 84 patients reported port-site recurrence in 1 of 40 patients treated by laparoscopic hysterectomy after a median 79-month follow-up¹⁰.

The non-randomised comparative study of 309 patients treated by laparoscopic or abdominal hysterectomy reported bladder dysfunction in less than 1% (1/165 and 1/144 respectively) of patients in both groups⁹.

Validity and generalisability of the studies

- Most of the studies only included patients with early stage endometrial cancer. The largest RCT included patients with disease stage I to IIA⁹. Four of the 5 RCTs included in the meta-analysis only included patients with FIGO stage I endometrial cancer^{1,2,4,5,7,8}. The remaining RCT included patients with stage I–III disease⁴. Of the 2 non-randomised comparative studies, 1 included patients with stage I or II disease and the other included all patients with endometrial cancer^{10,11}.
- In both non-randomised comparative studies, there was an over-representation of 'low-risk' tumours in the laparoscopic group^{10,11}.
- One study excluded patients who were scheduled to undergo laparoscopy but were converted to laparotomy¹⁰. This makes it difficult to compare rates of conversion to open surgery.
- Different laparoscopic techniques were used by different studies. Two studies reported that total laparoscopic hysterectomy was performed^{3,11} and 3 reported that laparoscopically assisted vaginal hysterectomy was performed^{4,10,12}.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Laparoscopic radical hysterectomy for early cervical cancer. NICE interventional procedures guidance 24 (2003). Available from www.nice.org.uk/ipg24
- Laparoscopic techniques for hysterectomy. NICE interventional procedures guidance 239 (2007). Available from www.nice.org.uk/IPG239

Technology appraisals

- None

Clinical guidelines

- None

Public health guidance

- None

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr D Barton, Mr M Maresh, Dr T Lopes, Miss K Singh, Mrs S Sundar (Royal College of Obstetricians and Gynaecologists).

Mr A Farthing (British Society for Gynaecological Endoscopy)

- Four Specialist Advisers described the procedure as being established practice and no longer new, and two described it as being a minor modification of an established procedure.
- The appropriate comparator is total abdominal hysterectomy with or without lymphadenectomy.
- Laparoscopic hysterectomies are being done in a variety of ways - laparoscopically assisted vaginal hysterectomy, laparoscopic hysterectomy, total laparoscopic hysterectomy.
- One Specialist Adviser noted that there is considerable controversy concerning the surgical management of pelvic and para-aortic lymph nodes in endometrial cancer, not only in the UK but internationally.

IP overview: Laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

- Adverse events reported in the literature include conversion to open surgery, respiratory difficulties, damage to abdominal or pelvic structures, port-site herniation and port-site metastasis. One Specialist Adviser reported an anecdotal adverse event of dehiscence of the vaginal vault after laparoscopic suturing.
- Three Specialist Advisers raised concern about use of the procedure in obese patients.
- Key efficacy outcomes include overall survival, recurrence rate, quality of life, operative time, length of hospital stay, and time to mobilisation.
- Case selection is important. Two Specialist Advisers stated that abdominal surgery rather than laparoscopic surgery may be more suitable for patients with a large uterus.
- Training in advanced laparoscopic skills is necessary to perform the procedure.
- One Specialist Adviser stated that there are agreed national guidelines for those endometrial cancers that can be operated on in cancer units and those that should be referred to cancer centres.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme were unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial is currently recruiting patients in Australia. The primary objective of this study is to assess disease-free survival at 4.5 years postoperatively for women with apparent stage I endometrial cancer, comparing patients who are randomised to receive total laparoscopic hysterectomy (TLH) and patients who are randomised to receive total abdominal hysterectomy (TAH). The estimated enrolment is 640 patients and the study is due to be completed in 2014.
- Several papers included in appendix A describe laparoscopic hysterectomy with robotic assistance.

References

1. Palomba S, Falbo A, Mocciaro R et al. (2009) Laparoscopic treatment for endometrial cancer: a meta-analysis of randomized controlled trials (RCTs). *Gynecologic Oncology* 112: 415–21.
2. Palomba S, Falbo A, Zullo F. (2009) Updating of a recent meta-analysis of randomized controlled trials to assess the safety and the efficacy of the laparoscopic surgery for treating early stage endometrial cancer. *Gynecologic Oncology* 114: 135–9.
3. Malzoni M, Tinelli R, Cosentino F et al. (2009) Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. *Gynecologic Oncology* 112: 126–33.
4. Tozzi R, Malur S, Koehler C et al. (2005) Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. *Journal of Minimally Invasive Gynecology* 12: 130–6.
5. Zorlu CG, Simsek T, Ari ES. (2005) Laparoscopy or laparotomy for the management of endometrial cancer. *Journal of the Society of Laparoendoscopic Surgeons* 9: 442–6.
6. Zullo F, Palomba S, Russo T et al. (2005) A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *American Journal of Obstetrics and Gynecology* 193: 1344–52.
7. Fram KM. (2002) Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. *International Journal of Gynecological Cancer* 12: 57–61.
8. Zullo F, Palomba S, Falbo A et al. (2009) Laparoscopic surgery vs laparotomy for early stage endometrial cancer: long-term data of a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 200: 296–99.
9. Walker JL, Piedmonte MR, Spirtos NM et al. (2009) Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *Journal of Clinical Oncology* 27: 5331–6.
10. Cho Y-H, Kim D-Y, Kim J-H et al. (2007) Laparoscopic management of early uterine cancer: 10-year experience in Asan Medical Center. *Gynecologic Oncology* 106: 585–90.

11. Obermair A, Manolitsas T, Leung Y et al. (2004) Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. *Gynecologic Oncology* 92: 789–93.
12. Kalogiannidis I, Lambrechts S, Amant F et al. (2007) Laparoscopy-assisted vaginal hysterectomy compared with abdominal hysterectomy in clinical stage I endometrial cancer: safety, recurrence, and long-term outcome. *American Journal of Obstetrics and Gynecology* 196: 248–50.
13. Logani S, Herdman A, Little J et al. (2008) Vascular “pseudo invasion” in laparoscopic hysterectomy specimens: a diagnostic pitfall. *American Journal of Surgical Pathology* 32: 560–5.

Appendix A: Additional papers on laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Barakat RR, Lev G, Hummer AJ et al. (2007). Twelve-year experience in the management of endometrial cancer: a change in surgical and postoperative radiation approaches. <i>Gynecologic Oncology</i> 105: 150–6.	n = 1312 (AH and LH) Median follow-up = 32 months.	Over a 12-year period, primary management of endometrial cancer changed to include increased use of laparoscopy with no significant difference in 5-year survival.	Results are not presented separately for LH.
Bell MC, Torgerson J, Seshadri-Kreaden U et al. (2008) Comparison of outcomes and cost for endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic techniques. <i>Gynecologic Oncology</i> 111: 407–11.	Non-randomised comparative study n = 110 Follow-up not reported.	The robotic approach took longer to perform but compared favourably with AH and LH with regard to cost and complications.	Length of follow-up not clear.
Boggess JF, Gehrig PA, Cantrell L et al. (2008) A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. <i>American Journal of Obstetrics and Gynecology</i> 199: 360–6.	Non-randomised comparative study n = 322 Follow-up not reported.	Robotic hysterectomy is feasible and preferable over AH and may be preferable over LH.	Length of follow-up not clear.
Chu CS, Randall TC, Bandera CA et al. (2003) Vaginal cuff recurrence of endometrial cancer treated by laparoscopic-assisted vaginal hysterectomy. <i>Gynecologic Oncology</i> 88: 62-65.	Case reports n = 3	Three patients with stage I, noninvasive or superficially invasive endometrial cancer with vaginal cuff recurrence within 9 months of treatment by laparoscopically assisted vaginal hysterectomy.	Case reports (vaginal cuff recurrence is already mentioned in table 2).
DeNardis SA, Holloway RW, Bigsby GE et al. (2008) Robotically assisted laparoscopic hysterectomy versus total abdominal hysterectomy and lymphadenectomy for endometrial cancer. <i>Gynecologic Oncology</i> 111: 412–7.	Non-randomised comparative study n = 162	Patients undergoing robotically assisted LH were younger, less obese and had less cardiopulmonary illness than patients previously treated with AH. Robotically assisted LH appears safe and feasible.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dierking E, Gogoi R, Adamcik S et al. (2008) Adrenal insufficiency after laparoscopic hysterectomy in a patient with primary antiphospholipid syndrome. <i>Obstetrics and Gynecology</i> 111: 495–8.	n = 1	Case of bilateral adrenal haemorrhage and subsequent adrenal insufficiency in a patient with anticardiolipin antibody syndrome. Patient was on anticoagulation treatment before LH.	Case report.
Fader AN, Michener CM, Frasure HE et al. (2009) Total laparoscopic hysterectomy versus laparoscopic-assisted vaginal hysterectomy in endometrial cancer: surgical and survival outcomes. <i>Journal of Minimally Invasive Gynecology</i> 16 (3) 333-339.	Non-randomised comparative study n = 104 Median follow-up = 52 months	Comparison of total laparoscopic hysterectomy (TLH) and laparoscopically assisted vaginal hysterectomy (LAVH). There was no difference in recurrence or survival rates between the groups. TLH had shorter operating times and less blood loss than LAVH.	Larger studies are included.
Faught W, Fung Kee Fung M. (1999) Port site recurrences following laparoscopically managed early stage endometrial cancer. <i>International Journal of Gynecological Cancer</i> 9: 256–8.	n = 1	Port site recurrence 7 months after LH.	Case report.
Garrett AJ, Nascimento MC, Nicklin JL et al. (2007) Total laparoscopic hysterectomy: The Brisbane learning curve. <i>Australian and New Zealand Journal of Obstetrics and Gynaecology</i> 47: 65–9.	Case series n = 120	Conversions to open surgery = 7% One serious adverse event – pelvic haematoma on postoperative day 17 (required drainage under ultrasound guidance)	Larger studies are included.
Gemignani ML, Curtin JP, Zelmanovich J et al. (1999) Laparoscopic-assisted vaginal hysterectomy for endometrial cancer: clinical outcomes and hospital charges. <i>Gynecologic Oncology</i> 73: 5–11.	Non-randomised comparative study n = 320 Median follow-up = 30 months	Patients in LH group had significantly shorter hospitalisation and fewer complications.	The majority of cases were AH.
Ghezzi F, Cromi A, Bergamini V et al. (2006) Laparoscopic management of endometrial cancer in nonobese and obese women: A consecutive series. <i>Journal of Minimally Invasive Gynecology</i> 13: 269-275.	Case series n = 101 Follow-up = 13 months	No difference was found in surgical outcome between obese and nonobese women.	Larger studies are included.
Ghezzi F, Cromi A, Bergamini V et al. (2006) Laparoscopic-assisted vaginal hysterectomy versus total laparoscopic hysterectomy for the management of endometrial cancer: a randomized clinical trial. <i>Journal of Minimally Invasive Gynecology</i> 13: 114-120.	RCT (LAVH vs TLH) n = 72 Median follow-up = 10 months	Women with high BMI may benefit from total laparoscopic approach in terms of shorter operating time, as the vaginal phase of LAVH can be technically challenging in the obese gynaecological patient.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Gil-Moreno A, Diaz-Feijoo B, Morchon S et al. (2006) Analysis of survival after laparoscopic-assisted vaginal hysterectomy compared with the conventional abdominal approach for early-stage endometrial carcinoma: a review of the literature. Journal of Minimally Invasive Gynecology 13: 26-35.	Non-randomised comparative study n = 370 Median follow-up = 38 months	Prognosis and survival were not affected by the laparoscopic vaginal approach.	Small number of patients in laparoscopic group.
Holub Z, Jabor A, Bartos P et al. (2002) Laparoscopic surgery for endometrial cancer: long-term results of a multicentric study. European Journal of Gynaecological Oncology 23: 305–310.	Non-randomised comparative study n = 221 Median follow-up = 34 months	There were significant differences between LH and AH with regard to tumour recurrence ($p = 0.99$) or recurrence-free survival ($p = 0.86$).	Larger studies are included.
Kim D Y, Kim MK, Kim JH et al. (2005) Laparoscopic-assisted vaginal hysterectomy versus abdominal hysterectomy in patients with stage I and II endometrial cancer. International Journal of Gynecological Cancer 15: 932-937.	Non-randomised comparative study n = 242 Median follow-up = 30 months	Three-year recurrence free survival rates: - LH = 97.5% - AH = 98.6%	Larger studies are included.
Kohlberger P, Nowotny G, Speiser P et al. (2007) Surgical treatment of endometrial cancer: does closure or non-closure of the vagina affect the local recurrence rate? Anticancer Research 27: 1589-1591.	Non-randomised comparative study n = 273 Mean follow-up = 24 months	The surgical technique of an open or closed vaginal cuff showed no significant impact on the local recurrence rate.	Larger studies are included.
Kuoppala T, Tomas E, Heinonen PK. (2004) Clinical outcome and complications of laparoscopic surgery compared with traditional surgery in women with endometrial cancer. Archives of Gynecology & Obstetrics 270: 25–30.	Non-randomised comparative study n = 80 Mean follow-up = 38 months	Postoperative complications were more common in AH group than LH group (55% vs 38%).	Larger studies are included.
Leiserowitz GS, Xing G, Parikh-Patel A et al. (2009) Laparoscopic versus abdominal hysterectomy for endometrial cancer. International Journal of Gynecological Cancer 19: 1370–6.	Non-randomised comparative study n = 12743 (8% LH) Mean follow-up = not reported	Patients undergoing LH were more likely to be younger and healthier and have stage I or grade 1 disease ($p < 0.0001$). Perioperative complications were significantly more common in AH patients.	Studies with longer follow-up are included.

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Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Lim S, Kim HS, Lee KB et al. (2008) Does the use of a uterine manipulator with an intrauterine balloon in total laparoscopic hysterectomy facilitate tumor cell spillage into the peritoneal cavity in patients with endometrial cancer? International Journal of Gynecological Cancer 18: 1145–9.	Case series n = 46 Median follow-up = 18 months	4% (2/46) of patients were upstaged to IIIA disease due to positive cytology conversion after the insertion of the uterine manipulator. However, neither had tumour recurrence during follow-up.	Larger studies are included.
Lowe MP, Johnson PR, Kamelle SA, et al. (2009) A multiinstitutional experience with robotic-assisted hysterectomy with staging for endometrial cancer. Obstetrics and Gynecology 114: 236–43.	Case series n = 405 Follow-up not reported.	Conversion to laparotomy = 7% Intraoperative complications = 4% Postoperative complications = 15% Fewer than 10 cases were required to achieve proficiency with robotic technique.	Larger studies are included.
Maenpaa J, Nyberg R. (2009) Port-site metastasis following laparoscopic hysterectomy and bilateral salpingo-oophorectomy for endometrial carcinoma. European Journal of Obstetrics & Gynecology and Reproductive Biology 143: 61–3.	Case report and review n = 7	Seven cases of port-site recurrence	Port-site recurrence is already mentioned in table 2.
Malur S, Possover M, Michels W et al. (2001) Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer – a prospective randomized trial. Gynecologic Oncology 80: 239–44.	RCT n = 70 Mean follow-up = 16.5 months	LH was associated with lower perioperative morbidity than AH. There were no significant differences in survival.	Small RCT with short follow-up.
Manolitsas TP and McCartney AJ. (2002) Total laparoscopic hysterectomy in the management of endometrial carcinoma. Journal of the American Association of Gynecologic Laparoscopists 9: 54–62.	Non-randomised comparative study n = 403 Follow-up not reported	Significantly more complications occurred in the AH group than the LH group (43% vs 17%, $p < 0.0001$). Mean postoperative hospital stay was significantly shorter for LH than for AH (4 vs 8 days, $p = 0.0001$).	Length of follow-up not clear.
Moreaux G, Estrade-Huchon S, Bader G et al. (2009) Five-millimeter trocar site small bowel eviscerations after gynaecologic laparoscopic surgery. Journal of Minimally Invasive Gynecology 16: 643–5.	Case report n = 2	Two cases of small bowel obstruction with evisceration through port site. One case was reduced locally and one required a segmental bowel resection.	Bowel obstruction and incisional hernia already mentioned in table 2.
Muntz HG, Goff BA, Madsen BL et al. (1999) Port-site recurrence after laparoscopic surgery for endometrial carcinoma. Obstetrics and Gynecology 93: 807-809.	n = 1	Port site recurrence 21 months after LH.	Port site recurrence already mentioned in table 2.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
O'Hanlan KA, Huang GS, Garnier AC et al. (2005) Total laparoscopic hysterectomy versus total abdominal hysterectomy: cohort review of patients with uterine neoplasia. Journal of the Society of Laparoendoscopic Surgeons 9: 277-286.	Non-randomised comparative study n = 105 Follow-up not reported	LH has few complications and is well tolerated in select patients.	Larger studies are included.
Sanjuan A, Hernandez S, Pahisa J et al. (2005) Port-site metastasis after laparoscopic surgery for endometrial carcinoma: two case reports. Gynecologic Oncology 96: 539-42.	n = 2	Two cases of port site metastasis at 39 and 48 months after LH.	Port site recurrence already mentioned in table 2.
Seamon LG, Backes F, Resnick K et al. (2008) Robotic trocar site small bowel evisceration after gynecologic cancer surgery. Obstetrics & Gynecology 112: 462-4.	n = 1	Small bowel obstruction after herniation through an 8 mm robotic port defect. The bowel was reduced locally and the fascial defect repaired without midline laparotomy or bowel resection.	Case report (incisional hernia is already mentioned in table 2)
Seamon LG, Cohn DE, Henretta MS et al. (2009) Minimally invasive comprehensive surgical staging for endometrial cancer: robotics or laparoscopy? Gynecologic Oncology 113: 36-41.	Non-randomised comparative study n = 181 Follow-up not reported	Robotic hysterectomy had shorter operating times and hospital stay, lower transfusion rate, and less frequent conversion to laparotomy than laparoscopic hysterectomy.	Larger studies are included.
Scribner DR, Walker JL, Johnson GA et al. (2001) Surgical management of early-stage endometrial cancer in the elderly: is laparoscopy feasible? Gynecologic Oncology 83: 563-8.	Non-randomised comparative study n = 125 Follow-up not reported	LH had equivalent blood loss, less postoperative infectious complications, lower rates of postoperative ileus and shorter length of hospital stay.	Larger studies are included.
Sonoda Y, Zerbe M, Smith A et al. (2001) High incidence of positive peritoneal cytology in low-risk endometrial cancer treated by laparoscopically assisted vaginal hysterectomy. Gynecologic Oncology 80: 378-382.	Non-randomised comparative study n = 377 Follow-up not reported	Treatment of low-risk endometrial cancer by laparoscopically assisted vaginal hysterectomy was associated with a higher incidence of positive peritoneal cytology compared with AH. This may be due to retrograde dissemination of cancer cells into the peritoneal cavity during uterine manipulation.	No follow-up.
Studies identified post-consultation			
Cardenas-Goicoechea J, Adams S, Bhat SB et al. (2010) Surgical outcomes of robotic-assisted surgical staging for endometrial cancer are equivalent to traditional laparoscopic staging at a minimally invasive surgical center. Gynecologic Oncology 117: 224-8.	Non-randomised comparative study n = 275 Follow-up =	Robotic-assisted versus conventional laparoscopic staging Mean operative time was longer in cases of robotic-assisted staging but blood loss was significantly lower. There were no significant differences in the rate of major complications, the time to discharge, readmission,	Larger studies are included

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	not reported	or reoperation rates.	
Eisenkop SM (2010) Total laparoscopic hysterectomy with pelvic/aortic lymph node dissection for endometrial cancer--a consecutive series without case selection and comparison to laparotomy. Gynecologic Oncology 117: 216–23.	Non-randomised comparative study n = 305 Follow-up = not reported	Total laparoscopic hysterectomy versus total abdominal hysterectomy Conversions to open surgery = 3% Laparoscopic group had a larger nodal yield, reduced blood loss, some reduction in complications, reduced hospital stay, statistically longer but clinically equivalent operative time.	Larger studies are included
Hahn H-S, Kim H-J, Yoon S-G et al. (2010) Laparoscopy-assisted vaginal versus abdominal hysterectomy in endometrial cancer. International Journal of Gynecological Cancer 20: 102–9.	Non-randomised comparative study n = 465 Mean follow-up = 40 months (laparoscopy group)	Laparoscopy versus laparotomy Grade and surgical stage were higher in laparotomy group than in the laparoscopy group. There were no significant differences in intraoperative or postoperative complications. Multivariate analysis showed no significant difference in survival between the two groups.	Larger studies are included
Santi A, Kuhn A, Gyr T et al. (2010) Laparoscopy or laparotomy? A comparison of 240 patients with early-stage endometrial cancer. Surgical Endoscopy 24: 939–43.	Non-randomised comparative study n = 240 Follow-up = not reported	Laparoscopy versus laparotomy Hospital stay was significantly shorter and estimated intraoperative blood loss was significantly lower in laparoscopic group.	Larger studies are included

Appendix B: Related NICE guidance for laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

Guidance	Recommendations
Interventional procedures	Laparoscopic radical hysterectomy for early stage cervical cancer. NICE interventional procedures guidance 24 (2003) (<i>under review – see below for updated provisional recommendations</i>) 1.1 Current evidence on the safety and efficacy of laparoscopic radical hysterectomy does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake laparoscopic radical hysterectomy should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's <i>Information for the Public</i> is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and longer-term efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking any further investigation at present. 1.2 Clinicians undertaking this procedure should undergo training as recommended by the Royal College of Obstetricians and Gynaecologists Working Party on Training in Endoscopic Surgery (www.rcog.org.uk). Laparoscopic radical hysterectomy for early stage cervical cancer. <i>Provisional revised recommendations (2010).</i> 1.1 Current evidence on the efficacy and safety of laparoscopic radical hysterectomy for early stage cervical cancer is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. 1.2 Patient selection should be carried out by a multidisciplinary gynaecological oncology team. 1.3 Advanced laparoscopic skills are required for this procedure and clinicians should undergo special training and mentorship. The Royal College of Obstetricians and Gynaecologists has developed an Advanced Training

	Skills Module, which is available from www.rcog.org.uk/curriculum-module/advanced-laparoscopic-surgery-excision-benign-disease. This needs to be supplemented by further training to achieve the skills required for laparoscopic radical hysterectomy for early stage cervical cancer. Laparoscopic techniques for hysterectomy. NICE interventional procedures guidance 239 (2007) 1.1 Current evidence on the safety and efficacy of laparoscopic techniques for hysterectomy (including laparoscopically assisted vaginal hysterectomy [LAVH], laparoscopic hysterectomy [LH], laparoscopic supracervical hysterectomy [LSH] and total laparoscopic hysterectomy [TLH]) appears adequate to support their use, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Clinicians should advise women that there is a higher risk of urinary tract injury and of severe bleeding associated with these procedures, in comparison with open surgery. 1.3 Advanced laparoscopic skills are required for these procedures, and clinicians should undergo special training and mentorship. The Royal College of Obstetricians and Gynaecologists has developed an Advanced Training Skills Module, 'Benign Gynaecological Surgery: Laparoscopy' (www.rcog.org.uk/index.asp?PageID=1951). This would need to be supplemented by further training in order to achieve the skills required for total laparoscopic hysterectomy.
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Appendix C: Literature search for laparoscopic hysterectomy (including laparoscopic total hysterectomy and laparoscopically assisted vaginal hysterectomy) for endometrial cancer

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	03/02/2010	Issue 1, 2010	2
Database of Abstracts of Reviews of Effects – DARE (CRD website)	03/02/2010	N/A	2
HTA database (CRD website)	03/02/2010	N/A	0
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	03/02/2010	Issue 1, 2010	0
MEDLINE (Ovid)	03/02/2010	1950 to January Week 3 2010	67
MEDLINE In-Process (Ovid)	03/02/2010	February 2, 2010	8
EMBASE (Ovid)	03/02/2010	1980 to 2010 Week 04	103
CINAHL (NLH Search 2.0 or EBSCOhost)	03/02/2010	N/A	7
BLIC (Dialog DataStar)	03/02/2010	N/A	0
Zetoc	03/02/2010	N/A	3

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Uterine Neoplasms/
2	Endometrial Neoplasms/
3	Carcinoma, Endometrioid/
4	((Uter* or Endomet* or womb) adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or dysplasis* or disease* or adenocanthom* or sarcom*)).tw.
5	or/1-4
6	exp laparoscopy/
7	exp laparoscopes/
8	laparoscop*.tw.
9	exp surgical procedures, Minimally Invasive/
10	or/6-9

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11	exp Hysterectomy/
12	(Hysterectom* or Hysterctom*).tw.
13	or/11-12
14	13 and 10
15	(lsh or lavh or larvh or tlh).tw.
16	15 or 14
17	16 and 5
18	Animals/ not Humans/
19	17 not 18
20	limit 19 to ed=20090501-20100203