Recurrence and survival after laparoscopy versus laparotomy without lymphadenectomy in early-stage endometrial cancer: long-term outcomes of a randomised trial.

Reijntjes, B.; Suijlichem, M. van; Woolderink, J.M.; Bongers, M.Y.; Reesink-Peters, N.; Paulsen, L.; ... ; Mourits, M.J.E.

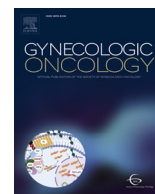# Recurrence and survival after laparoscopy versus laparotomy without lymphadenectomy in early-stage endometrial cancer: Long-term outcomes of a randomised trial

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HIGHLIGHTS

- Long-term outcomes of TLH vs TAH without lymphadenectomy in early EC are reported.
- There were no significant differences in DFS, OS and DSS, 5 years postoperatively.
- No port-site or wound metastases were found after TLH or TAH.
- Our findings support the widespread use of TLH without lymphadenectomy for early EC.

ARTICLE INFO

ABSTRACT

Background. Laparoscopic hysterectomy is accepted worldwide as the standard treatment option for early-stage endometrial cancer. However, there are limited data on long-term survival, particularly when no lymphadenectomy is performed. We compared the survival outcomes of total laparoscopic hysterectomy (TLH) and total abdominal hysterectomy (TAH), both without lymphadenectomy, for early-stage endometrial cancer up to 5 years postoperatively.

Methods. Follow-up of a multi-centre, randomised controlled trial comparing TLH and TAH, without routine lymphadenectomy, for women with stage I endometrial cancer. Enrolment was between 2007 and 2009 by 2:1 randomisation to TLH or TAH. Outcomes were disease-free survival (DFS), overall survival (OS), disease-specific survival (DSS), and primary site of recurrence. Multivariable Cox regression analyses were adjusted for age, stage, grade, and radiotherapy with adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI) reported. To test for significance, non-inferiority margins were defined.

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Survival
Lymphadenectomy

Results. In total, 279 women underwent a surgical procedure, of whom 263 (94%) had follow-up data. For the TLH (*n* = 175) and TAH (*n* = 88) groups, DFS (90.3% vs 84.1%; aHR[recurrence], 0.69; 95%CI, 0.31–1.52), OS (89.2% vs 82.8%; aHR[death], 0.60; 95%CI, 0.30–1.19), and DSS (95.0% vs 89.8%; aHR[death], 0.62; 95%CI, 0.23–1.70) were reported at 5 years. At a 10% significance level, and with a non-inferiority margin of 0.20, the null hypothesis of inferiority was rejected for all three outcomes. There were no port-site or wound metastases, and local recurrence rates were comparable.

Conclusion. Disease recurrence and 5-year survival rates were comparable between the TLH and TAH groups and comparable to studies with lymphadenectomy, supporting the widespread use of TLH without lymphadenectomy as the primary treatment for early-stage, low-grade endometrial cancer.

1. Introduction

Worldwide, endometrial cancer (EC) is the sixth most common malignancy in women and the second most common gynaecological malignancy, with more than 400,000 new cases recorded in 2020 (1). The incidence is steadily increasing due to the increased prevalence of established risk factors such as obesity and ageing (2,3). Given that postmenopausal bleeding is an early symptom, 80% of women have early-stage disease at the time of diagnosis (3,4), and the prognosis of EC is relatively good, having a 5-year survival rate of 84% (5). The treatment of choice for early-stage, low-grade EC is surgical removal of the uterus with bilateral salpingo-oophorectomy (BSO) (4). These patients are at low risk of lymph node metastasis, and given that clinical benefit is therefore unlikely, systematic lymphadenectomy has been omitted from national guideline (6,7).

Hysterectomy was traditionally performed by laparotomy, but since the introduction of minimally invasive surgery, there has been a tendency to perform the procedure laparoscopically. Randomised clinical trials have established the surgical safety of total laparoscopic hysterectomy (TLH) compared to total abdominal hysterectomy (TAH) (8–10), showing TLH to be associated with less blood loss, less pain, shorter hospital stay, and faster recovery, as well as better quality of life at 3 months postoperatively (8–11). Although these favourable short-term outcomes have made TLH a globally accepted standard treatment for early-stage, low-grade EC, there is only limited information on its long-term safety (12,13). In 2012 and 2017, long-term data were published in the LAP2 (12) and LACE (13) trials, respectively. Although these showed that the overall survival (OS) and disease-free survival (DFS) after laparoscopic surgery were comparable to those after laparotomy (12,13), both advocated routine lymphadenectomy, even for early-stage, low-grade EC (8,9). Lymphadenectomy in early stage EC is now increasingly out of favour, at least in Europe, making this study relevant (4,6,7).

In this study, we evaluated the 5-year follow-up data from the earlier Dutch TLH-TAH trial comparing TLH and TAH without lymphadenectomy in early stage, low grade EC (10). Our primary hypothesis was that TLH would be as safe as TAH with respect to DFS outcomes during long-term follow-up. The secondary outcomes were the OS, the disease-specific survival (DSS), and the site of primary recurrence.

2. Methods

2.1. Study design and participants

This is a follow-up study using data from a multi-centre, randomised controlled TLH-TAH trial that compared outcomes for TLH and TAH without lymphadenectomy in the Netherlands (10). Women with clinical stage I, low-risk (grade 1–2) EC, were randomised on a 2:1 basis to either TLH or TAH, both performed without lymphadenectomy, between February 2007 and January 2009. The primary outcome was the major complication rate of TLH compared to TAH performed by experienced surgeons. The design of the trial and the requirements for participating centres and surgeons have been described elsewhere

(14). The trial concluded that there was no significant difference in the major complication rate between the TLH and TAH treatment groups, with both experiencing favourable short-term outcomes (10).

According to national guidance, based on the Post-operative Radiation Therapy for Endometrial Carcinoma (PORTEC)-I criteria (15), histopathological results were discussed in multidisciplinary tumour meetings and used to determine the indication for adjuvant treatment. Follow-up was performed every 3–4 months during the first 2 years, every 6 months in the third year, and annually thereafter to 5 years after surgery (15,16). The current study used the 5-year follow-up data collected from all 19 participating centres.

The study was conducted in accordance with the Medical Research Involving Human Subjects Acts (WMO). Patients gave their written informed consent for follow-up to 5 years after surgery. The current study is registered in the clinical Dutch trial register with an updated trial number (NL9097).

2.2. Data collection

Patient characteristics at the start of randomisation (before surgery) were obtained from the Dutch TLH-TAH study (10). Follow-up data were primarily collected from medical records, but in the event of incomplete data, general practitioners were approached to provide the missing data.

2.3. Study outcomes and definitions

The primary outcome was the 5-year DFS (5y-DFS), calculated as the time interval from the date of hysterectomy to the date of first recurrence. Patients without disease recurrence after 5 years, who died from other causes, or who were lost to follow-up, were censored at that time. Secondary outcomes were the 5-year OS (5y-OS), the 5-year DSS (5y-DSS), and the primary site of recurrence. The 5y-OS and the 5y-DSS were recorded as the time intervals from the date of hysterectomy to the dates of death from any cause and EC, respectively. Primary site of recurrence was classified as port-site or wound metastasis only, local recurrence only (i.e., vaginal vault), regional recurrence only (i.e., pelvic), distant metastasis only, or multiple sites. Since the study population was predefined, and its size was determined based on the original primary outcome measure (major complication rate), these long-term outcomes are by definition secondary outcome measures, and no power-analysis was performed (10).

2.4. Statistical analysis

Data were analysed on an intention-to-treat basis. The 5y-DFS, 5y-OS, and 5y-DSS were estimated using the non-parametric Kaplan–Meier method (17). The effect of surgical technique (TLH versus TAH) on these outcomes was evaluated by Cox regression analysis. All hazard ratios (HRs) were adjusted for the well-known prognostic factors for EC recurrence: age, International Federation of Gynaecology and Obstetrics (FIGO) 1988 stage (I versus II–IV), grade of differentiation ('low-grade' 1–2 versus 'high-grade' 3) and adjuvant radiotherapy (yes versus no).

In this way, adjusted HRs (aHRs) and related 95% confidence intervals (95% CIs) were estimated. Next, based on these aHRs critical margins of non-inferiority were estimated at a 10% level. Analyses were performed using IBM SPSS version 27.0 for Windows (IBM Corp., Armonk, NY, USA).

3. Results

In total, 263 of the 279 randomised patients (94%) could be included in this analysis. The patient flow chart is summarised in Figure 1, which shows that 16 patients were lost to follow-up (10 in the TLH group and 6 in the TAH group). Patients included in the current analysis were comparable to those who were lost to follow-up (Table 1). The median follow-up duration was 5.0 years in the TLH group and 4.8 years in the TAH group (Table 2). In total, 20.7% in the TLH group and 27.3% in the TAH group received adjuvant radiotherapy.

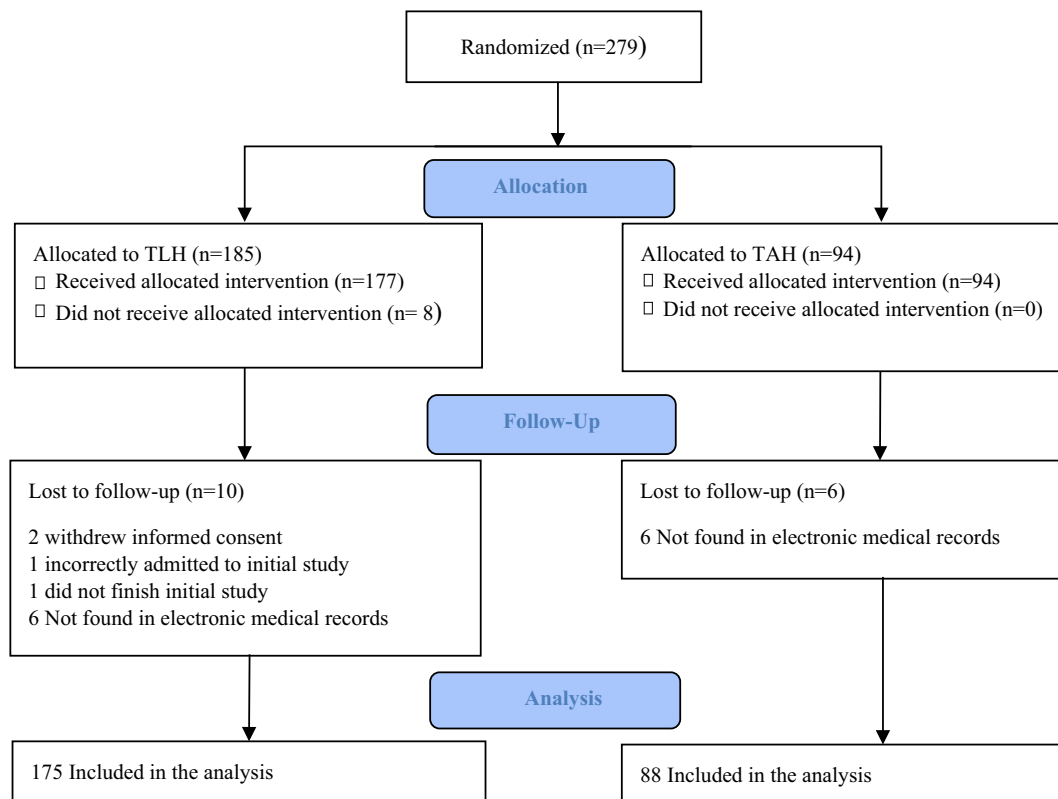### 3.1. Disease-free survival, overall and disease-specific survival

During the 5-year follow-up period, 29 patients developed recurrence, of which 16 (9.7%) were in the TLH group and 13 (15.9%) were in the TAH group (Table 2). The median time to recurrence was 1.5 year after TLH and 1.1 year after TAH, but there were no cases of port-site or wound metastases. Two patients in each group had recurrence in only the vaginal vault. Additionally, of the patients with multiple recurrence sites, one in the TLH group and four in the TAH group had concurrent disease of the vaginal vault.

The 5y-DFS were 90.3% in the TLH group and 84.1% in the TAH group (Table 2, Figure 2A). The aHR for EC recurrence was 0.69 (95%CI, 0.31–1.52) (Table 3).

Table 1
Patient, disease, and treatment characteristics at time of surgery.

	Initial study (n = 279) (10)		Follow-up study (n = 263)	
	TLH (n = 185)	TAH (n = 94)	TLH (n = 175)	TAH (n = 88)
Age in years median (min–max) at randomisation	62 (40–89)	63 (39–86)	62 (40–89)	64 (39–86)
Histological EC subtype				
No dysplasia or malignancy	11 (5.9)	1 (1.1)	10 (5.7)	1 (1.1)
Complex atypical hyperplasia	24 (13.0)	7 (7.4)	22 (12.6)	7 (8.0)
Endometrioid adenocarcinoma	147 (79.5)	83 (88.3)	141 (80.6)	77 (87.5)
Papillary adenocarcinoma	1 (0.5)	2 (2.1)	1 (0.6)	2 (2.3)
Sarcoma	1 (0.5)	1 (1.1)	1 (0.6)	1 (1.1)
FIGO 1988 stage *				
I	130 (87.2)	75 (87.2)	124 (86.7)	69 (86.3)
II	15 (10.1)	8 (9.4)	14 (9.8)	8 (10.0)
III	2 (1.3)	2 (2.3)	3 (2.1)	2 (2.5)
IV	2 (1.3)	1 (1.2)	2 (1.4)	1 (1.3)
Grade of differentiation *				
Low-grade (1, 2)	139 (93.3)	81 (94.2)	133 (93.0)	75 (93.8)
High-grade (3)	10 (6.7)	5 (5.8)	10 (7.0)	5 (6.2)
Adjuvant radiotherapy provided	38 (20.5)	25 (26.6)	36 (20.7)	24 (27.3)

Baseline characteristics are reported as N (%), unless specified otherwise, for the initial trial and the current study populations. Abbreviations: EC = endometrial cancer; FIGO = International Federation of Gynaecologists and Obstetricians 1988; TAH = total abdominal hysterectomy; TLH = total laparoscopic hysterectomy. * Patients with dysplasia or complex atypical hyperplasia in the final uterine specimen were not given a FIGO stage or grade.

Fig. 1. CONSORT diagram for the long-term oncological survival analysis.
TLH = total laparoscopic hysterectomy. TAH = total abdominal hysterectomy.

Table 2
Outcomes for disease-free, overall, and disease-specific survival at 5 years and the primary site of recurrence.

	TLH ($n = 175$)	TAH ($n = 88$)
Follow-up time in years (median (IQR))	5.0 (3.6–5.3)	4.8 (3.3–5.4)
Time to recurrence in years (median (IQR))	1.5 (0.4–4.6)	1.1 (0.5–3.2)
5-year disease-free survival (%)	90.3	84.1
5-year overall survival (%)	89.2	82.8
5-year disease-specific survival (%)	95.0	89.8
Primary site of recurrence		
Port-site/wound metastases	0	0
Only vaginal vault	2	2
Only regional	1	1
Only distant metastases	10	4
Multiple sites	3	6

Abbreviations: IQR = Interquartile range.

Overall, 38 patients (19 per treatment arm) died during the 5 years of follow-up, giving 5y-OS rates of 89.2% for the TLH group and 82.8% for the TAH group (Table 2, Figure 2B). The aHR for overall mortality was 0.60 (95%CI, 0.30–1.19) (Table 4). Similarly, 18 patients (9 per treatment arm) died due to EC during the 5 years of follow-up, giving estimated 5y-DSS rates of 95.0% in the TLH group and 89.8% in the TAH group (Table 2, Figure 2C). The aHR for EC-specific mortality did not reach a statistically significant difference (0.62; 95%CI, 0.23–1.70) (Table 5).

At a 10% significance level, and with a non-inferiority margin of 0.20, we could reject the null hypothesis of inferiority for all three outcomes. At a 5% significance level, and at the same non-inferiority margin of 0.20, only OS was significantly non-inferior, while for the other outcomes the null hypothesis of inferiority could not be rejected (Table 6).

4. Discussion

In this multi-centre randomised controlled trial of patients with early-stage, low-grade EC, the 5y-DFS was 90.3% after TLH and 84.1%
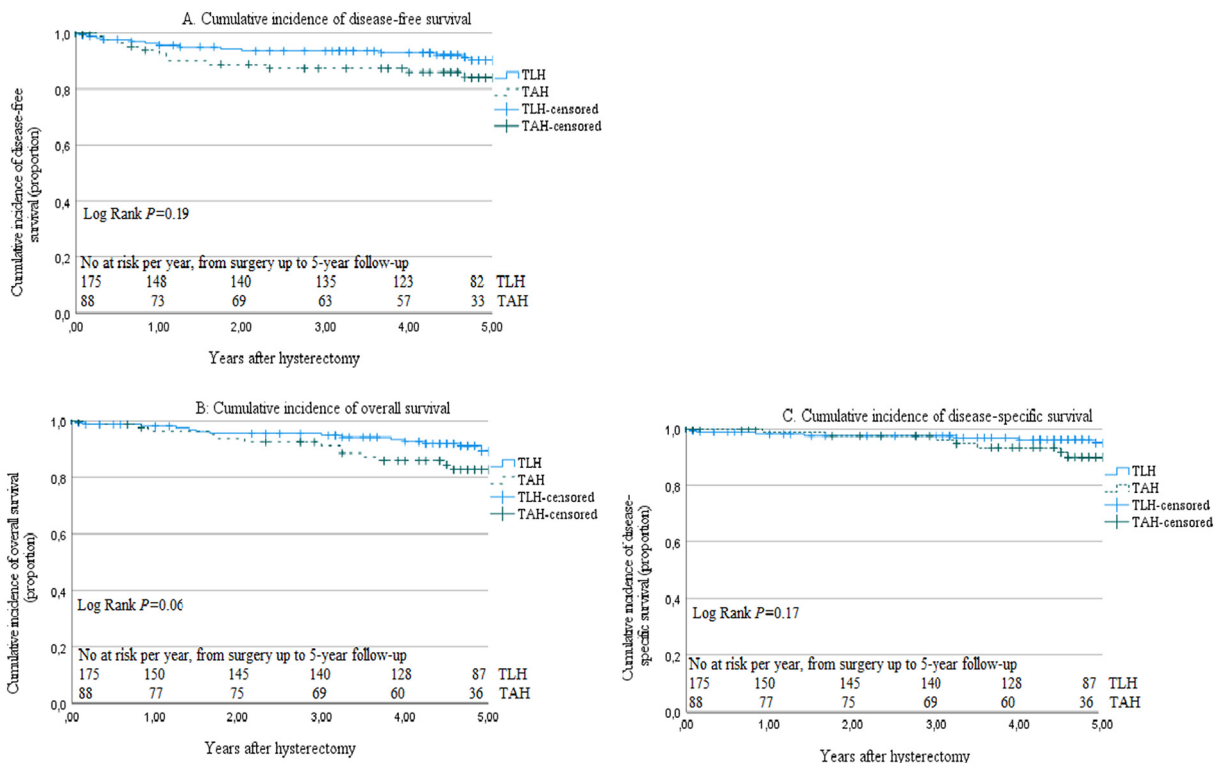
Table 3
Multivariable Cox regression analysis for the 5-year disease recurrence of TLH versus TAH ($n = 223$).

	aHR[recurrence]	95% CI
TLH versus TAH	0.69	0.31–1.52
Age	1.04	0.99–1.08
FIGO stage II–IV versus I	6.33	2.21–18.12
Grade 3 versus 1–2	2.25	0.71–7.13
Radiotherapy yes versus no	0.64	0.21–1.99

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; FIGO = International Federation of Gynaecologists and Obstetricians 1988; TLH = total laparoscopic hysterectomy; TAH = total abdominal hysterectomy.

after TAH, with no significant difference between groups ($P = 0.19$). This is the first randomised study assessing long-term outcomes after treatment by laparoscopic hysterectomy without lymphadenectomy for early-stage, low-grade EC. The 5y-DFS was based on disease recurrence in 29 patients: 16 (9.7%) in the TLH group and 13 (15.9%) in the TAH group. Disease recurrence also remained comparable between the TLH and TAH groups after adjustment for factors known to affect EC recurrence, the aHR[recurrence] being 0.69 (95%CI, 0.31–1.52). The multivariate analyses for overall mortality (5y-OS aHR[death], 0.60; 95%CI, 0.30–1.19) and EC specific mortality (5y-DSS aHR[death], 0.62; 95%CI, 0.23–1.70) also failed to show any significant differences between the TLH and TAH groups.

Another important outcome parameter is the primary site of recurrence. Vaginal vault recurrence and port-site metastasis are rare outcomes in early-stage disease but these have nevertheless been described. These are considered a major concern when treating EC by laparoscopy instead of open treatment. However, we found no port-site metastases or wound metastases in either group. Furthermore, vaginal vault recurrence occurred in nine patients, and of these, three were in the TLH group and six were in the TAH group. Four patients (TLH 2; TAH 2) had only isolated vaginal vault recurrence, but five (TLH 1; TAH 4) had vaginal vault recurrences accompanied by distant

Fig. 2. Cumulative incidence of disease-free (A), overall (B), and disease-specific (C) survival by treatment group up to 5 years after surgery.
TLH = total laparoscopic hysterectomy; TAH = total abdominal hysterectomy.

Table 4
Multivariable Cox regression analysis for the 5-year overall mortality of TLH versus TAH (n = 223).

	aHR[death]	95% CI
TLH versus TAH	0.60	0.30–1.19
Age	1.06	1.02–1.10
FIGO stage II–IV versus I	2.51	0.98–6.44
Grade 3 versus 1–2	2.89	1.05–7.91
Radiotherapy yes versus no	0.67	0.28–2.05

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; FIGO = International Federation of Gynaecologists and Obstetricians 1988; TLH = total laparoscopic hysterectomy; TAH = total abdominal hysterectomy.

Table 5
Multivariable Cox regression analysis for the 5-year disease-specific mortality of TLH versus TAH (n = 223).

	aHR[death]	95% CI
TLH versus TAH	0.62	0.23–1.70
Age	1.02	0.97–1.08
FIGO stage II–IV versus I	2.73	1.75–9.95
Grade 3 versus 1–2	3.93	1.03–14.97
Radiotherapy yes versus no	0.93	0.22–3.89

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; FIGO = International Federation of Gynaecologists and Obstetricians 1988; TLH = total laparoscopic hysterectomy; TAH = total abdominal hysterectomy.

metastases and/or regional recurrences. Despite this, we found no evidence that TLH increased the risk of vaginal relapse over TAH. This pattern of disease recurrence is in line with existing literature (12,13,18).

Considering only early-stage, low-grade EC, few studies have assessed recurrence rates or DFS after laparoscopic surgery. There have only been two other multi-centre RCTs with a large enough power to provide sufficient long-term evidence: the US LAP2 trial (12) and the Australian LACE trial (13).

The LAP2 trial, which included 2616 women, uncovered estimated 5-year recurrence rates of 11.61% and 13.68% after TAH and TLH, respectively. Although these results did not meet the non-inferiority criteria based on the initial assumption of 15% recurrence, they provide strong evidence that TLH may be an acceptable alternative to TAH based on the estimated difference in recurrence of only 2.07%. Although they did include patients with any type of EC histology, recurrence after TLH was higher than in our study. It should also be noted that the conversion rate was 25% in the LAP2 trial, which can be explained by the routine use of lymphadenectomy (98% with TLH and 99% with TAH).

In the LACE trial of 760 women with a follow-up time of 4.5 years, equivalent DFS was shown between the TAH (81.3%) and TLH (81.6%) groups, meeting the criteria for equivalence. This trial found lower DFS rates than in our study, but these could be explained by their inclusion of 'death from any cause' and 'new primary tumour'. The main contrast to our study, however, was that half of all patients in the LACE trial received concomitant lymph node dissections.

Disease recurrence in three other RCTs with smaller sample sizes (fewer than 100 participants) has been summarised in a recent

meta-analysis, which found no significant difference in the risk of disease recurrence between TLH and TAH (19).

4.1. Strengths and limitations

The current randomised controlled multi-centre TLH-TAH trial provides data in a real-life setting in the Netherlands. The procedures were performed in both teaching and non-teaching hospitals and only by trained, experienced surgeons. This RCT is one of the most prominent studies of the short-term safety of TLH, being key to the implementation of TLH for early-stage EC in Europe. The results of this follow-up study complement the present literature, mainly in Europe, where lymphadenectomy is not a standard surgical procedure for early-stage, low-grade EC.

Some important limitations should also be considered. Data are incomplete, with 16 patients being lost to follow-up. During the follow-up period, some hospitals merged and new electronic systems were implemented, so patient data were lost despite efforts to collect data from general practitioners as well. The original study was designed and powered to compare major surgical complication rates between treatment groups and not powered for survival rates. Minimal invasive surgery proved not to be safe for all gynecologic malignancies as was shown for radical hysterectomy in cervical cancer which showed disturbing results with lower overall- and disease-free survival rates (20,21). It is essential to prove that minimal invasive surgery for endometrial cancer is safe on the long-term after these data have been published. Although not sufficiently powered for survival outcomes, our study is the largest study reporting the survival data comparing TLH versus TAH without lymphadenectomy. Because this was a follow-up study on a secondary outcome, no power analysis had been performed, and rather than formally testing for non-inferiority, results were reported by providing critical thresholds for non-inferiority margins that would result in rejection of inferiority, as well as 95% CIs.

5. Conclusion

This is the first study on long-term survival among women with early-stage EC undergoing TLH or TAH without routine lymphadenectomy. Women showed comparable DFS rates after both surgical treatments. Combined with previous reports of improved short-term surgical outcomes, these results support the widespread use of TLH as the primary treatment for early-stage, low-grade EC.

Author contributions

Conceptualization: GHdB, MJEM, BR, MvS
Data curation: BR, MvS, GHdB, MJEM, JMW, MYB, NRS, LP, PJvdH, AAK, MJAA, BS, TS, FHMPT, PJMvK, JAFH, DB
Formal analysis: BR, MvS, GHdB, MJEM, JMW, MYB, NRS, LP, PJvdH, AAK, MJAA, BS, TS, FHMPT, PJMvK, JAFH, DB
Investigation: BR, MvS, GHdB, MJEM JMW, MYB, NRS, LP, PJvdH, AAK, MJAA, BS, TS, FHMPT, PJMvK, JAFH, DB
Methodology: BR, MvS, GHdB, MJEM, GL, JMW, MYB, NRS, LP, PJvdH, AAK, MJAA, BS, TS, FHMPT, PJMvK, JAFH, DB
Project administration: GHdB, MJEM
Software: GHdB, GL

Table 6
Critical non-inferiority margins.

Out-come	Log aHR	Log aHR 95% CI	1 sd (log aHR)	Log aHR 10% 1-sided CI	aHR 10% 1-sided CI	Critical margin of non inferiority (10% level)	Log aHR 5% 1-sided CI	aHR 5% 1-sided CI	Critical margin of non inferiority (5% level)
DFS	−0.371	(−1.171,0.4187)	0.4055	<0.1480	<1.159	0.159	<0.298	<1.347	0.347
OS	−0.511	(−1.204,0.1740)	0.3515	<−0.061	<0.941	0	<0.069	<1.071	0.071
DSS	−0.478	(−1.470,0.5306)	0.5104	<0.1753	<1.192	0.192	<0.364	<1.439	0.439

Shown are the log aHR and 95% confidence interval (CI); one standard deviation (SD) of log aHR; the 1-sided CI (mean plus 1.65, 1.28 SDs for significance level 5%, 10%); and the critical margin of non-inferiority (1-sided CI limit on natural scale minus 1; zero if negative).

Declaration of Competing Interest

The authors declare no conflicts of interest.

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