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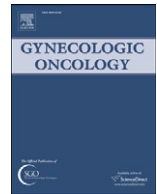
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## Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: A randomised trial

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### ABSTRACT

**Objective.** To determine the cost effectiveness of total laparoscopic hysterectomy (TLH) versus total abdominal hysterectomy (TAH) in early stage endometrial cancer alongside a multicenter randomised controlled trial (RCT).

**Methods.** An economic analysis was conducted in 279 patients (TLH  $n = 185$ ; TAH  $n = 94$ ) with early stage endometrial cancer from a societal perspective, including all relevant costs over a three month time horizon. Health outcomes were expressed in terms of major complication-free rate and in terms of utility based on women's response to the EQ-5D. Comparisons of costs per major complication-free patient gained and costs with utility gain and costs were made, using incremental cost effectiveness ratios.

**Results.** The mean major complication-free rate and median utility scores were comparable between TLH and TAH at three months. TLH is more costly intraoperatively ( $\Delta\$1.129$ ) and less costly postoperatively in-hospital ( $\Delta\$-1.350$ ) compared to TAH. Incremental costs per major complication-free patient were  $\$-52$ . Higher cost ( $\$249$ ) were generated while no gains in utility ( $-0.02$ ) were observed for TLH compared to TAH. Analysing utility at six weeks, incremental costs per additional point on the EQ-5D scale were  $\$1.617$ .

**Conclusion.** TLH is cost effective compared to TAH, based on major complication-free rate as measure of effect. Along with future cost saving strategies in laparoscopy, TLH is assumed to be cost effective for both effect measures. Therefore and due to comparable safety, TLH should be recommended as a standard-of-care surgical procedure in early endometrial cancer.

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### Introduction

Endometrial cancer is the third most common cancer in women in Western countries, accounting for 6 to 9% of malignancies in women with a peak incidence at the age of 55–65 years. The standard treatment in early stage endometrial cancer patients is total

abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH) with or without lymphadenectomy through a vertical midline incision. A good alternative and less invasive approach for patients with an early stage disease might be a total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TLH). Three randomised controlled trials showed that complication rates are similar for both treatment modalities or resulted in fewer complications for TLH in this patient group, with a shorter hospital stay, less blood loss, less pain and a faster resumption of daily activities in favour of laparoscopy compared to laparotomy [1–3]. The lower complication rate in the Dutch trial when compared with the American GOG study and Australian LACE trial is probably due to the fact that patients in the Netherlands underwent a hysterectomy and bilateral salpingo-oophorectomy only and not a complete surgical staging including pelvic and para-aortic lymphadenectomy [3].

The perception that laparoscopic procedures are more costly than open procedures has been a major reason for the slow acceptance of advanced (level 3) laparoscopic surgery [4]. Laparoscopy is assumed

**Abbreviations:** BMI, Body Mass Index; CEA, Cost Effectiveness Analysis; CI, Confidence Interval; CRF, Case Record Form; CUA, Cost Utility Analysis; CVZ, College of Health Insurances; EQ-5D, Euroqol-5D; FIGO, The International Federation of Gynecology and Obstetrics; ICER, Incremental Cost Effect Ratio; RCT, Randomised Controlled Trial; SD, Standard Deviation; TAH, Total Abdominal Hysterectomy and Bilateral Salpingo-Oophorectomy; TLH, Total Laparoscopic Hysterectomy and Bilateral Salpingo-Oophorectomy; QALY, Quality Adjusted Life Year; ZonMw, Dutch Organization for Health Research and Development.

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to be more costly due to longer duration of surgery, expensive surgical disposable equipment and additional costs in case of conversion to laparotomy. It is important to know how these cost differences between TLH and TAH relate to the differences in clinical effects. A combination of the development of expensive new treatments, the limited budgets available and the increasing demands on the health system has led to a need to evaluate the costs in addition to clinical effects, in order to make rational decisions regarding the acceptance of new treatments.

In a recent published review, the benefits of shorter hospital stay after laparoscopy seemed to compensate for the increased procedure related costs [5]. Thus if laparoscopic hysterectomy has benefits for the patients over laparotomy, it might be a promising alternative. However, given the methodological impediments of the majority of studies included in this review, no firm conclusions could be drawn. Importantly, randomised controlled trials are the most rigorous way of determining the cost effectiveness of a treatment avoiding all sorts of bias [6]. Therefore a broader, societal perspective is needed, including all relevant costs and clinical effects for determining implications for practice. The aim of this study is to evaluate the cost effectiveness of the two surgical approaches (TLH versus TAH), carried out alongside a multicenter randomised controlled trial, complying with all guidelines [7,8].

## Methods

### Study design

A detailed description of the study protocol has been reported elsewhere [9] and is summarized here briefly. This multi-center prospective randomised clinical phase three trial included 26 gynaecologists in 21 centers in the Netherlands. The gynaecological surgeons were allowed to participate in the study only after achieving sufficient laparoscopic skills for performing a TLH, according to a predefined assessment [9]. We included women with histologically proven endometrioid adenocarcinoma, grade 1 or 2, or complex atypical hyperplasia, clinically confined to the uterine corpus. Exclusion criteria were any non-endometrioid adenocarcinoma histological types, uterine size larger than that expected at twelve weeks pregnancy and cardiopulmonary contraindications for laparoscopy or laparotomy. After given informed consent, eligible patients were randomised in a 2:1 allocation to receive TLH or TAH. Amongst 283 randomised patients, 187 were assigned to the TLH group and 96 to the TAH group during the study period of 23 months. In each arm two patients were randomised, although it was known before randomisation that they did not fulfil the inclusion criteria. These patients were not included in the intention-to-treat analysis (Fig. 1) [1]. The study coordinator had no access to data during the study. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). Ethics approval was obtained from local research ethics committees. Patients were informed that there was no proven advantage for either TLH or TAH in early endometrial cancer patients so far, and therefore this study was performed. All women gave written, informed consent before randomisation. The trial was registered in the clinical Dutch trial register, number NTR821.

### Economic evaluation

#### Design

An economic evaluation was conducted alongside the randomised clinical trial and performed from a societal perspective, meaning all relevant costs both inside and outside the hospital were included. A cost effectiveness analysis (CEA) was undertaken to evaluate the balance between costs and effects of both treatment modalities over

a 3 months time horizon. The CEA depicts the additional costs per major complication-free patient that need to be invested in the situation that TAH is replaced by TLH. In addition, a cost utility analysis (CUA) was undertaken to evaluate the balance between costs and utility of both surgical techniques. The CUA depicts the additional costs per extra point on the utility scale. Finally, cost effectiveness planes were constructed depicting 5000 bootstrap replications of the trial data. From these estimates, a confidence interval and an acceptability curve were generated, representing the probability that an intervention (TLH) is most effective over a range of thresholds [8,10,11].

#### Assessment of cost

Resource use data included procedure costs (time, housing, equipment, disposables, overhead), hospital stay and costs incurred during the postoperative period (Table 1). A case record form (CRF) was used to gather these in-hospital medical costs. Cost components were valued according to standard Dutch guidelines for economic evaluation (College Voor Zorgverzekering, CVZ 2004). The price level used was that of 2008 and costs were calculated in Euros (€) and converted to US Dollars (\$) at the conversion rate of 31-12-2008. Actual costs were estimated for the laparotomy and laparoscopy (Table 1). The patient questionnaire was used to collect information on costs of additional home care, professional as well as informal. Informal care was valued by using shadow prices (Table 1). Because of the composition of the patient group, characterized by women with a median age of 63 years (Table 2), productivity losses were not included in the economic evaluation. Since no differences regarding complication rate and quality of life were expected between the two study arms after three months, a time horizon of three months was considered to be sufficient for evaluation of costs. As a consequence, discounting was not applied.

#### Assessment of effects

Our primary measure of effect was major complication-free rate. Data and details on patients with a major complication were published previously [1]. All complications were recorded intra- and postoperatively until three months after surgery for each patient. After completing of inclusion complication data were re-checked on site for possible inaccuracies or incompleteness. Data on major complication-free rate was complete for all cases. The secondary measure of effect was utility, and was added, to increase the comparability between our results and the results from other studies. Utility reflects differences in health-related quality of life based on women's response to the Euroqol-5D (EQ-5D) questionnaire at baseline and up to three time points after surgery (6 weeks, 3 months and 6 months) [1,12]. For a subgroup of 25 patients EQ-5D questionnaires were sent one year after surgery. Scores were calculated using Dolans algorithm, based on the preferences elicited from the general UK population [13]. No imputation techniques were used since baseline characteristics and health outcomes did not differ between completers and non-completers.

#### Sensitivity analysis

A sensitivity analysis was conducted to assess how differential costs would have changed if all laparoscopic procedures had been undertaken with a cheaper disposable vaginal tube (i.e., decreasing the price of the Mc Cartney tube by 50%) and shortening of the hospital stay with one day in the laparoscopy group, based on an expert opinion of evolving laparoscopic practice. In this scenario we assumed that there would be no impact on health outcomes from this change in policy. In addition, a sensitivity analysis was performed with the effect measure utility (EQ-5D) and total costs at six weeks and was compared with a previous literature.

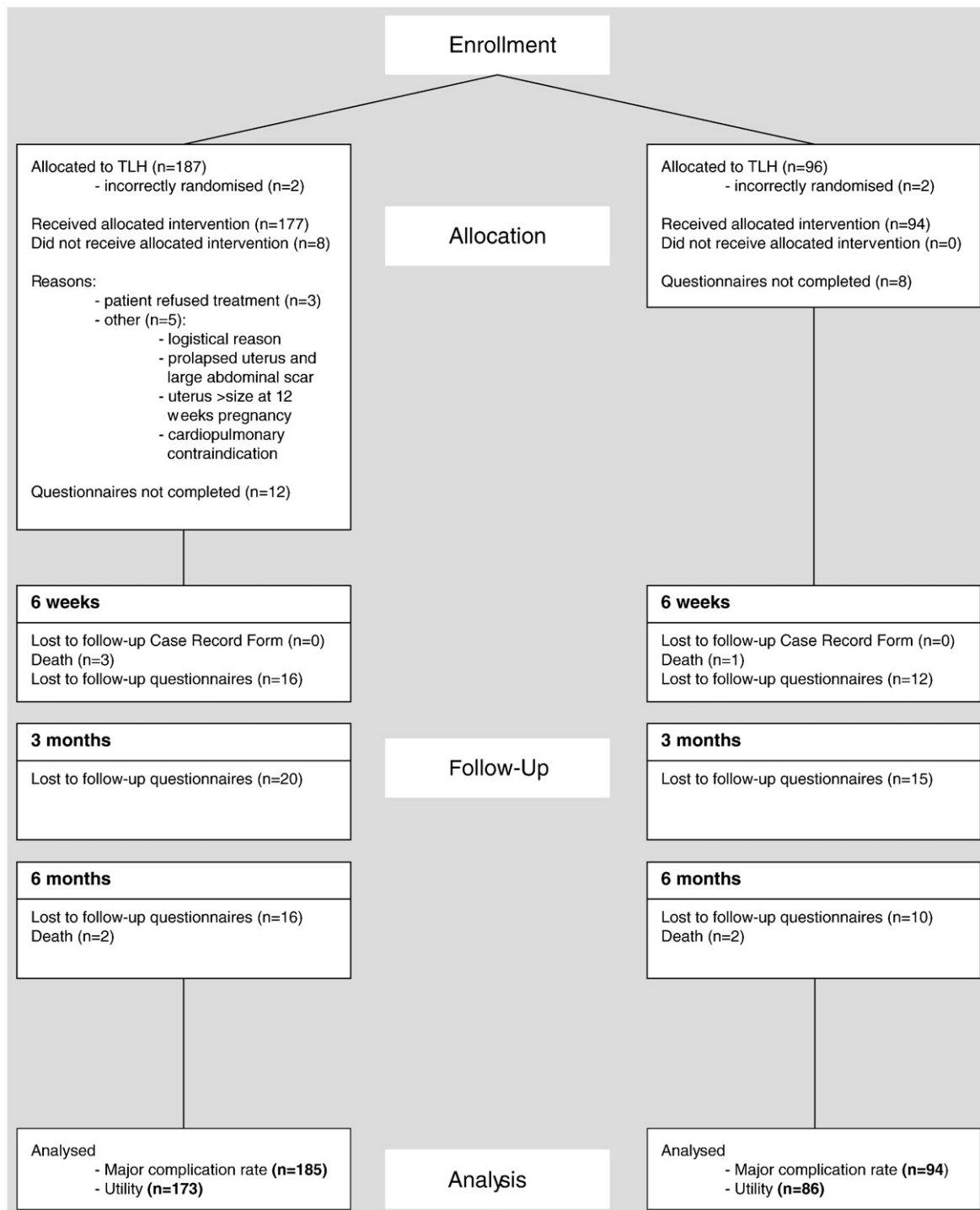


Fig. 1. Flowchart patients.

### Statistical analysis

All patients were analysed on an intention-to-treat basis. Descriptive data are reported as mean (standard deviation), 95% confidence interval (CI), median and range, or number of patients and percentage. For clinical and demographical data, a comparison between groups for categorical variables was made by  $\chi^2$  test or the Fisher exact test when appropriate. In other situations, nonparametric analysis was performed: the Mann–Whitney *U* test was used to test differences between groups. The *P*-values <0.05 were considered to indicate statistical significance (2-tailed test). Analyses

were performed using Microsoft Office Excel (2003) and the SPSS software package, version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

### Results

#### Study population

Baseline characteristics were equally distributed between treatment arms in the intention-to-treat-analysis (Table 2). The median age was 63 years (39 to 89) and the median BMI was 29 kg/m<sup>2</sup> (17 to

**Table 1**  
Resources and quantity unit per treatment arm.

Item	Unit	Price	Method	TLH mean (SD) <sup>a</sup>	TAH mean (SD)	Difference
Operative procedure				1653 (486)	524 (238)	1129
Operating time (personnel)	Per minute	4404	CVZ 2004	524 (172)	362 (165)	162
Disposables	Per set	1410	Cost price	894 (412)	0 (0)	894
Overhead/housing	OK time	10%/35%	HVK 2004: 64–66	235 (78)	162 (73)	73
Hospital stay				1656 (1402)	3007 (1656)	–1350
General hospital/ University medical center (3:1)	Per day	562.83	HvK 2004: 70–72			
Additional homecare				1558 (2718)	1511 (2126)	47
Homecare (housework)	Per hour	40.43	HvK 2004: 94–95	279 (925)	368 (761)	–89
Homecare (nursing)	Per hour	61.16	HvK 2004: 94–95	826 (1842)	732 (1387)	94
Time costs informal care	Per hour	12.56	HvK 2004: 107–111	420 (902)	340 (593)	80
Home served meals	Per time	9.16	Mean cost price	32 (151)	73 (251)	–41

<sup>a</sup> SD = standard deviation.

55). In total, 117 (42.2%) patients were obese (>BMI 30 kg/m<sup>2</sup>). Comorbidity (chronic disease and/or previous malignancy) was reported in nearly 60% of included patients. Based on the final pathology report, the majority (84.2%) had International Federation of Gynaecologists & Obstetricians (FIGO) stage I endometrioid adenocarcinoma or complex atypical hyperplasia.

#### Cost comparison

The cost components used for the cost evaluation with accompanying quantity units are depicted in Table 1. A mean difference of \$1.129 in surgical procedure costs reflects the significant longer duration of surgery in the TLH arm (115 min; 35 to 267) versus the TAH arm (71 min; 31 to 239) ( $p < 0.001$ ) (not in Table) and the extra costs of the use of disposables with laparoscopy. The total costs for the duration of hospital stay differed with \$1.350 in favour of laparoscopy. Patients treated by laparoscopy had a shorter (2 days; 1 to 25) hospital stay after surgery than patients treated by laparotomy (5 days; 3 to 32) ( $p < 0.001$ ) (not in Table). Information about additional home care was completed in 72.0% of the patients. Patients treated by laparoscopy experienced more hours of additional home care than after a laparotomy, reflecting the fact that due to an earlier discharge for laparoscopy patients relatively longer home care (nursing) is needed.

**Table 2**  
Baseline characteristics of patients (N (%))<sup>a</sup>.

Baseline	Overall N = 279	TLH N = 185	TAH N = 94
Median age (range) years	63 (39–89)	62 (40–89)	63 (39–86)
BMI (median; range) kg/m <sup>2</sup>	29 (17–55)	29 (17–55)	28 (19–48)
>30 kg/m <sup>2</sup> (2 missing)	117 (42.2)	80 (43.5)	37 (39.8)
Co-morbidity (incl. previous malignancy)	165 (59.1)	107 (57.8)	58 (61.7)
Previous abdominal surgery	78 (28.0)	55 (29.7)	23 (24.5)
Histological subtype			
No dysplasia/malignancy	12 (4.3)	11 (6.0)	1 (1.1)
Complex atypical hyperplasia	31 (11.2)	24 (13.0)	7 (7.4)
Endometrioid adenocarcinoma	230 (82.7)	147 (79.9)	83 (88.3)
Papillary adenocarcinoma	3 (1.1)	1 (0.5)	2 (2.1)
Sarcoma	2 (0.7)	1 (0.5)	1 (1.1)
(1 missing)			
FIGO <sup>b</sup> stage			
I	205 (87.2)	130 (87.2)	75 (87.2)
II	23 (9.8)	15 (10.1)	8 (9.3)
III	4 (1.7)	2 (1.3)	2 (2.3)
IV	3 (1.3)	2 (1.3)	1 (1.2)
(1 missing)			

<sup>a</sup> Unless otherwise specified.<sup>b</sup> International Federation of Gynaecologists & Obstetricians.

#### Health outcomes

There was no difference observed in the mean major complication-free rate between TLH (85.4%) and TAH (85.1%) ( $p = 0.95$ ) [1]. Data on major complication-free rate was complete for all cases. At six weeks, median EQ-5D utility scores were 0.81 (–0.2 to 1.0) for TLH versus 0.80 (0.3 to 1.0) for TAH. At three months, median scores for TLH were 0.81 (–0.4 to 1.0) compared to 0.85 (0.6 to 1.0) for TAH. Median Quality adjusted life years (QALYs) were comparable in both arms at three months, 0.19 (–0.06 to 0.23) for TLH and 0.19 (0.10 to 0.23) for TAH, adjusted for baseline (not in Table). The overall response rate on the questionnaires was 90% (range 88% to 93%) at various assessment points. No significant differences in compliance were observed between the treatment arms. Data about EQ-5D was complete in 83% of patients. Four patients died (grade 5) within six weeks after surgery; three of these (3/185; 1.6%) died after TLH and one after TAH (1/94; 1.1%) (Fig. 1). Two patients died of progressive metastatic disease, one patient died most probably due to a pulmonary embolism five days after surgery, and one died because of progressive hypoxia leading to a hypoxic coma, with already existing cardiopulmonary problems.

#### Cost effectiveness

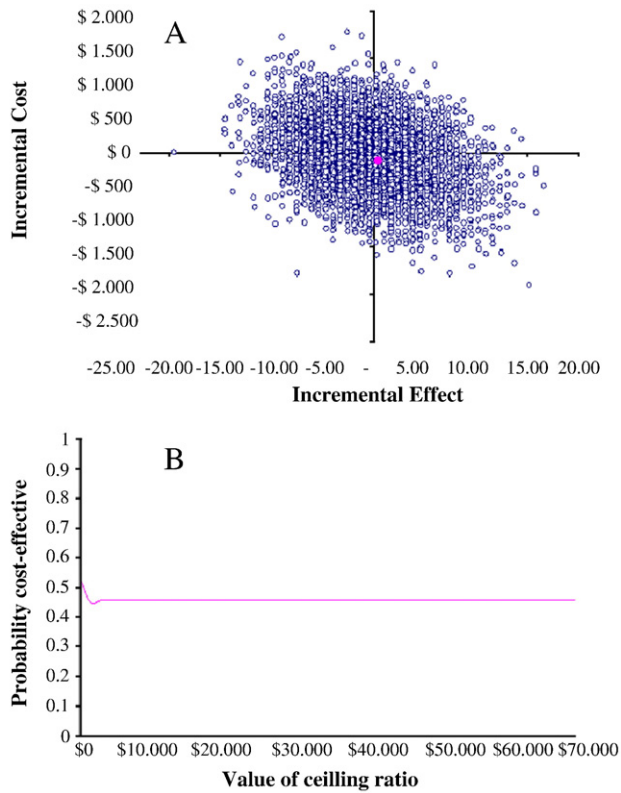
With a mean difference of \$–8 in costs and a mean difference of 0.16% in major complication-free rate, the incremental cost effect ratio (ICER) generated is \$–52 (–988 to 1.106) for laparoscopy, based on the bootstrap simulations (TLH N = 142; TAH N = 70).

From the bootstrapped cost effectiveness plane (Fig. 2A) it can be seen that the ICER is located at the south eastern quadrant. The acceptability curve (Fig. 2B) showed that the probability that TLH is more cost effective in terms of major complications than TAH is never above 53%. A mean difference of \$249 in costs and a mean difference of –0.02 in utilities generate an ICER of \$–15.604 for laparoscopy, based on the bootstrap simulations (TLH N = 134; TAH N = 67). This ICER is located in the North West quadrant (Fig. 3A). The acceptability curve (Fig. 3B) showed that the probability that TLH is more cost effective than TAH in terms of utilities is never above 31%.

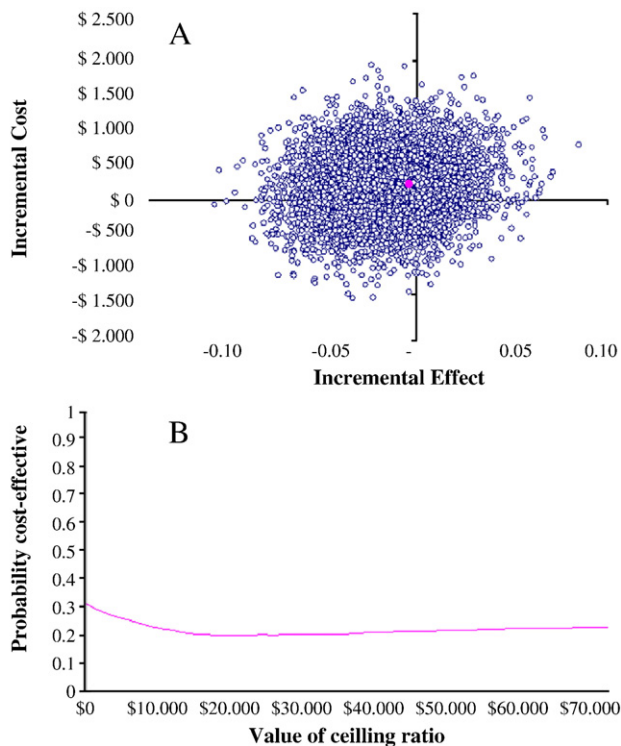
#### Sensitivity analysis

In case of reducing disposable costs and duration of hospital stay in the TLH arm, the mean difference (TLH–TAH) in costs was increased to \$–681 in favour of TLH and the ICER for laparoscopy to \$–4.229 (–3.138 to 1.837) (Fig. 4A) with major complication-free rate as the measure of effect. For the CUA, the mean difference in costs was increased to \$–455 in favour of TLH and the ICER for laparoscopy to \$28.527 (–228.345 to 240.075) (Fig. 4B). In case of analysing utility at six weeks instead of three months (Fig. 4C), the bootstrapped samples shifted to the eastern quadrants, meaning more effects (0.05)

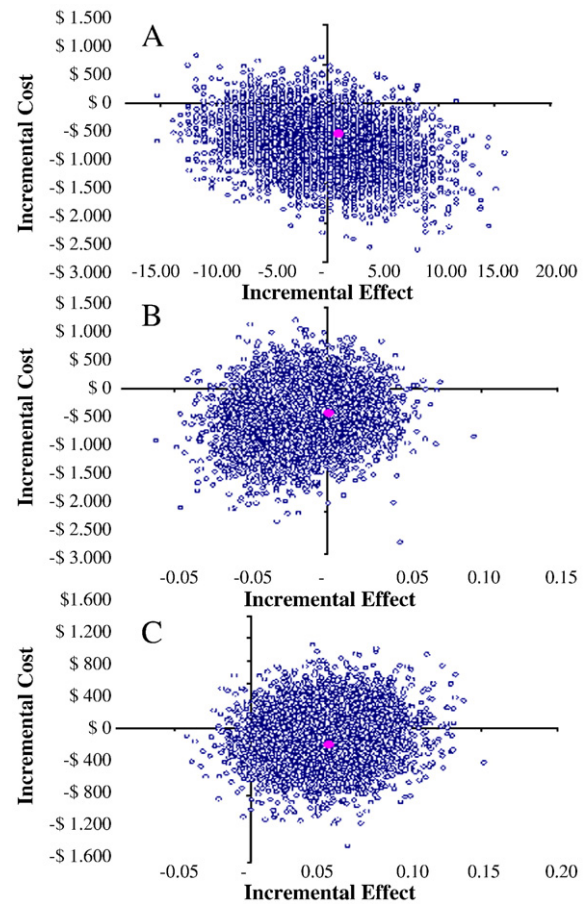




**Fig. 2.** A Cost effectiveness planes for major complication-free rate; B acceptability curve for major complication-free rate. \* = scatterplot of the estimated (joint density) of incremental costs and incremental effects of TAH versus TLH, based on 5000 bootstrap re-samples of the original trial data. The main dot represents the base estimate of incremental costs and effects, all other individual dots represent bootstrap replications. The two quadrants right from the Y axis represent the replications where TLH is more effective than TAH, and vice versa for left from the Y axis. Dots below the X axis represent lower costs of TLH versus TAH and vice versa for under the X axis.



**Fig. 3.** A Cost effectiveness planes for utility; B acceptability curve for utility.



**Fig. 4.** A for major complication-free rate (reducing costs); B for utility (reducing costs); and C for utility (at 6 weeks).

for laparoscopy with lower costs (\$−100), generating an ICER of \$−1.617 (−38.709 to 25.793).

## Discussion

From this cost effectiveness analysis it can be concluded that TLH appears to be preferable over the conventional approach by TAH as an amount of \$52 will be saved per additional major complication-free patient. The higher operative procedure costs of TLH were compensated by the lower costs for hospital stay when compared to TAH. Major complication-free rate was higher and utility scores were lower in the TLH group when compared to the TAH group. With respect to utility, higher costs were generated while no gains in utility were observed for TLH compared to TAH.

To our knowledge, this is the first multi center randomised study comparing cost effectiveness of laparoscopy and laparotomy in early stage endometrial cancer patients. The fact that TLH is considered as being preferable, based on the major complication-free rate as the measure of effect, is consistent with a recently published review [5]. In this review, comparing costs and cost effectiveness between laparoscopic and abdominal hysterectomies in twelve prospective controlled trials [14–25], laparoscopic hysterectomy pointed in the direction of cost effectiveness due to a lower major complication rate, with higher costs in the laparoscopy group when compared to laparotomy. However, all studies were performed in patients with a benign indication for the removal of the uterus, and used different variants of laparoscopic techniques. Besides, due to flexibility in design, definitions, and analytical modes for costs in the previous studies, a rigorously set up, well-designed RCT is a prerequisite to evaluate the cost effectiveness of the two surgical

approaches (TLH versus TAH) in early endometrial cancer patients and complies with all guidelines for costs studies.

If all laparoscopic procedures had been undertaken with cheaper disposables because of expected changes in cost price, TLH would be considered more cost effective. This was illustrated in Figs. 4A and B, in which all points shifted to the lower quadrants of the planes when compared to Figs. 2 and 3. The same phenomenon was seen when utility six weeks after surgery was taken into account instead of three months. This time horizon was chosen to compare the utility scores with a previous RCT by Sculpher et al. on laparoscopy in patients with a benign indication for the removal of the uterus [21]. The differences in median utility scores between the two surgical techniques was comparable at six weeks, but both utility scores were lower in our study (TLH: 0.81 versus TAH: 0.80) when compared to the study of Sculpher et al. (TLH: 0.87 versus TAH: 0.88). The fact that all patients in our study are entrusted with a malignant disease might have had more impact on the quality of life than the surgical technique itself.

The limitations of our study are the short follow-up of three months and consequently not taking survival into account as an effect measure. Because of this three month period, utility is taken as the effect measure instead of the Quality Adjusted Life Years. The time horizon of three months was chosen since no differences regarding complications and quality of life were expected between the two study arms after three months. A clinical significant difference in prognostic impacts between the two surgical techniques on patients with early endometrial cancer is not expected. From the recent preliminary data it can be concluded that patients staged by laparoscopy or laparotomy had similar recurrence rates and patterns and an estimated three-year survival of about 90% [26,27].

Furthermore, in a random sample of twenty-five patients included in the trial, we analysed costs and cost effectiveness and found no differences in costs and effects between treatment groups at twelve months. However, these results need to be interpreted carefully given the small number of patients in that pilot.

We used a societal perspective to estimate the costs of both surgical procedures. Any differential impact of the procedures on time away from the usual activities, including paid employment, might be reflected in differential productivity costs. This randomised trial collected data on the rate of returning to paid or volunteer work. These showed that the rate of returning to work at six weeks after surgery did not differ between patients in the TLH (37/167; 22.2%) and TAH (22/82; 26.8%) groups ( $p = 0.42$ ) [1]. The fact that the return rates were comparable and reported in small groups due to a high median age of patients would not have altered the relative cost effectiveness of these two procedures.

The results of this randomised study on laparoscopy versus laparotomy for the early stage endometrial cancer can be used to guide further implementation of laparoscopic hysterectomy. In our published RCT with major complication rate as the primary outcome measure, we concluded that there is no evidence of a lower complication rate in laparoscopy when compared to laparotomy in patients with the early stage endometrial cancer. Nevertheless, laparoscopy has the advantage of a shorter hospital stay, less pain after surgery and a quicker resumption of daily activities [1]. The question rises, should we implement this surgical technique as the standard approach for this patient category? Since safety was comparable between both interventions, the treatment related outcome and cost effectiveness will become decisive. In the here presented analysis, we concluded that TLH is cost effective compared to TAH, based on major complication-free patients as a measure of effect. Although the laparoscopic technique itself requires attention, the quality of the implementation of the laparoscopic intervention depends not only on the surgeon but also on the surgical environment, including the operating team, and the preoperative and postoperative care. Moreover, further development, experience and improvement of laparoscopic equipment are to be expected when compared to the

conventional approach. This advancement of the laparoscopic equipment and techniques together with optimizing the efficiency in surgical teams and post operative care might lead to the improvement of the surgical outcome in laparoscopy patients in the future. This prospect of a shorter hospital stay was included in a sensitivity analysis, resulting in an even more cost effective approach. Along with potential cost saving strategies in laparoscopic surgical equipment, TLH is cost effective and due to comparable safety should be recommended as a standard-of-care surgical approach for the early stage endometrial cancer. Based on the results of the study presented here and this future perspective, policy makers might be able to make a rational decision for acceptance of this new laparoscopic treatment for the early stage endometrial cancer with improved health gain and lower costs.

### Role of funding source

The sponsor (Dutch Organization for Health Research and Development; ZonMw) of the study reviewed and approved the study design, but had no role in collecting, analysing, or interpreting the data, writing the report, or deciding to submit the paper for publication. The authors had full access to all data in the study after the completion of inclusion and external data monitoring. All authors participated in writing the report. The corresponding author had final responsibility for the decision to submit for publication.

### Authors' contributions

All authors participated in the study design, and/or recruited patients, and/or collected data. CB coordinated the study and CB and KV analysed the data. CB drafted the manuscript, and all authors contributed to the review and revision. All authors have seen and approved the final version.

### Conflict of interest statement

The authors declare that they have no competing interests.

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