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Laparoscopic hysterectomy is preferred over laparotomy in early endometrial cancer patients, however not cost effective in the very obese

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ABSTRACT

Background: Total laparoscopic hysterectomy (TLH) is safe and cost effective in early stage endometrial cancer when compared to total abdominal hysterectomy (TAH). In non-randomised data it is often hypothesised that older and obese patients benefit most from TLH. Aim of this study is to analyse whether data support this assumption to advice patients, clinicians and policy makers.

Methods: Data of 283 patients enrolled in a randomised controlled trial comparing TAH versus TLH in early stage endometrial cancer were re-analysed. Randomisation by sequential number generation was done centrally, with stratification by trial centre. Using multivariate analysis, predictors of major complications and conversions to laparotomy were assessed. For the cost effectiveness analysis, subgroups of patients were constructed based on age and body mass index (BMI). For each subgroup, costs per major complication-free patient were estimated, using incremental cost effect ratios (extra costs per additional effect).

Results: Older (odds ratio (OR): 1.05; 1.01–1.09) and obese (OR: 1.05; 1.01–1.10) patients had a higher risk to develop complications, for both groups. In obese (OR: 1.17; 1.09–1.25) patients and patients with a previous laparotomy (OR: 3.45; 1.19–10.04) a higher risk of conversion to laparotomy was found. For patients >70 years of age and patients with a BMI over 35 kg/m^2, incremental costs per major complication-free patients were €16 and €54 for TLH compared to TAH, respectively.

Conclusion: In general, TLH should be recommended as the standard surgical procedure in early stage endometrial cancer, also in patients >70 years of age. In obese patients with a BMI >35 kg/m^2 TLH is not cost effective because of the high conversion rate. A careful consideration of laparoscopic treatment is needed for this subgroup. Surgeon experience level may influence this choice.

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1. Introduction

Endometrial cancer is the third most common cancer in women in Western countries, accounting for 6–9% of all cancer types in women.[1] Predominantly, endometrial cancer occurs in postmenopausal women and 90% of the patients are over 50 years of age.[2–4] The incidence increases in overweight individuals, and almost half of the patients have a body mass index (BMI) >30 kg/m^2. In addition, a significant number of patients present with co-morbidity. Because postmenopausal bleeding is an early sign, the majority (75%) of patients are diagnosed at an early stage. Standard treatment for patients with early endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH) with or without lymph node dissection through a vertical midline incision. The role of laparoscopy has been discussed in several randomised reports for various gynaecological disorders and for endometrial cancer as well.[5–16] We recently performed a randomised controlled trial comparing total laparoscopic hysterectomy (TLH) by proven skilled surgeons and TAH, which indicated that TLH is cost effective without evidence of benefit in terms of complications. Furthermore, TLH was associated with significantly less blood loss, less use of pain medication, a shorter hospital stay, and a faster recovery than TAH.[2,17] In literature, it is often hypothesised that obese and elder patients do benefit more from TLH than younger patients.[18–20] The aim of the current analysis is to test whether this hypotheses is supported by our data from this randomised trial.

2. Patients and methods

2.1. Study design and patients

A detailed description of the study protocol has been reported previously.[21] This study concerned a multicentre prospective randomised clinical phase 3 trial, with 24 certified gynaecologists participating in 21 centres.[2] The standard surgical approach TAH was compared to the experimental surgical procedure TLH. Early stage endometrial cancer patients (endometrioid adenocarcinoma grade 1 or 2, clinically stage I disease), age 18 years and older were eligible for this trial. Eligible patients, enrolled by the participating gynaecologists, were randomly allocated to the intervention group (TLH) or control group (TAH). Randomisation was done via a computerised, unbalanced (2:1) method, favouring TLH to obtain more data on the experimental laparoscopic procedure. Randomisation by sequential number generation was done centrally in alternate blocks of six and three participants, with stratification by trial centre. Study coordinators, patients, gynaecologists and members of the panel were not masked to intervention after assignment.[2,21] Amongst 283 randomised patients (TLH $n = 187$; TAH $n = 96$), 279 (TLH $n = 185$; TAH $n = 94$) were included in the intention-to-treat analysis (Fig. 1). 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. 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). The protocol was registered in the clinical Dutch trial register number NTR821.

2.2. Methods

2.2.1. Assessment of effects

Our primary measure of effect was major complication-free rate (i.e. the percentage of patients without major complications). Since this concerns a secondary analysis, we focused on the main health outcome, major complication-free rate, only. The results of the primary outcome measure were published previously.[2] The occurrence of a conversion (from laparoscopy to laparotomy) was reported in the case record form (CRF). No imputation techniques were used since baseline characteristics and the health outcome did not differ between complete and missing data.[17]

2.2.2. Assessment of costs

Resource use data included procedure costs (time, housing, equipment, disposables, and overhead), hospital stay and costs incurred during the postoperative period. A CRF was used to gather these in-hospital medical costs. Further specification of resource units and valuation was reported previously.[17] The patient questionnaires were used to collect information on costs of additional home care, professional as well as informal.[17] Because of the composition of the patient group, characterised by women >60 years (Table 1), productivity losses were not included in the economic evaluation. In the present study, total costs and effects were calculated up to 6 weeks after surgery.

2.2.3. Design of the cost effect analysis (CEA)

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 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. Costs and incremental cost effect ratio (ICER) for major complications for complete cost effect pairs were calculated. With regard to complication rate, both costs and results were re-calculated to the level of 100 patients. Finally, cost-effectiveness planes were constructed depicting 5000 bootstrap replications of the selected subgroups.

2.3. Statistical analysis

All patients were analysed according to the intention-to-treat principles. Univariate logistic regression analyses, adjusted for treatment (i.e. TLH or TAH) were performed with a patient with major complication(s) or a patient in the TLH group who underwent a conversion to laparotomy as dependent variables and the baseline characteristics age, BMI, previous laparotomy, co-morbidity and International Federation of Gynaecologists and Obstetricians (FIGO) stage as independent variables. Odds ratios (OR's) and 95% confidence intervals (95% CIs) were calculated. Multivariate logistic analysis was

Table 1 – Patient and disease characteristics.

	N (%)[a]		
	Overall N = 279	Total laparoscopic hysterectomy (TLH) N = 185	Total abdominal hysterectomy (TAH) N = 94
Age (median; range) years	63 (39–89)	62 (40–89)	63 (39–86)
BMI[b] (median; range) kg/m^2 (two missing)	29 (17–55)	29 (17–55)	28 (19–48)
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 (one missing)	2 (0.7)	1 (0.5)	1 (1.1)
FIGO[c] 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 (one missing)	3 (1.3)	2 (1.3)	1 (1.2)

[a] Unless otherwise specified.
[b] Body mass index.
[c] International Federation of Gynaecologists and Obstetricians.

performed by using a backward step model with major complication or conversion to laparotomy as dependent variables and the statistically significant related variables, as assessed in the univariate logistic regression analysis, as independent variables. Variables were excluded from the model if $p \geqslant 0.05$.

In accordance with the assessed predictors from multivariate analysis, independent predictors were selected to create subgroups for the cost effectiveness analysis. One outlier in the TLH group due to extreme long hospitalisation and additional home care was deleted from the age subgroup, to prevent distortion of cost-effectiveness in this relatively small group. The mean total cost of this outlier was €15.234, whereas mean costs in the total group without the outlier was €3.500 (1.446–8.200).

All tests were two-sided and probability values of <0.05 were considered to be statistically significant. Analyses were performed using the SPSS software package, version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (2003).

3. Results

3.1. Study group and surgeons

Baseline characteristics were equally distributed between both treatment arms (Table 1). Median age was 63 years (39–89) and median BMI 29 kg/m^2 (17–55). Co-morbidity (chronic disease and/or previous malignancy) was reported in nearly

Table 2 – Regression analyses model on health outcomes.[a]

	Univariate analyses			Multivariate analysis		
Patients with major complications (n = 41)	OR[a]	95% CI[b]	p-value	OR	95% CI	p-value
Age (per unit years)	1.05	1.01–1.08	**0.009**	1.05	1.01–1.09	**0.007**
BMI[c] (per unit kg/m^2)	1.05	1.01–1.09	**0.025**	1.05	1.01–1.10	**0.019**
Previous laparotomy	1.82	0.91–3.63	0.090			
Co-morbidity	1.59	0.78–3.22	0.199			
FIGO[d] advanced stage (II–IV)	2.37	0.98–5.76	0.057			
Conversions (n = 20)	OR	95% CI	p-value	OR	95% CI	p-value
Age (per unit years)	0.99	0.94–1.04	0.740			
BMI (per unit kg/m^2)	1.16	1.09–1.24	**<0.001**	1.17	1.09–1.25	**<0.001**
Previous laparotomy	3.36	1.31–8.66	**0.012**	3.45	1.19–10.04	**0.023**
Co-morbidity	0.88	0.35–2.24	0.791			
FIGO advanced stage (II–IV)	0.96	0.21–4.50	0.963			

[a] Adjusted for surgical technique; odds ratio.
[b] Confidence interval.
[c] Body mass index.
[d] International Federation of Gynaecologists and Obstetricians; bold signifies $p < 0.05$.

60% of the included patients. Previous abdominal surgery had been performed in 78 (28.0%) patients. Based on the final pathology report, 12 (4.3%) patients had no hyperplasia, 31 (11.2%) patients had complex atypical hyperplasia, 230 (82.7%) had endometrioid adenocarcinoma, and in 5 (1.8%) patients papillary adenocarcinoma or sarcoma was diagnosed. In total, 205 (87.2%) patients were diagnosed with early stage endometrial cancer (FIGO stage I) and 30 (12.8%) patients with advanced stage disease (FIGO $\geqslant$II).

Of the 24 certified surgeons, 16 did perform a TLH in patients with a BMI >35 kg/m^2. The weighted median of operating obese patients in relation to the total amount of laparoscopy patients per surgeon is 13.8% (0.0–67.0) (not in table).

3.2. *Predictors of major complications and conversions*

In multivariate analysis, a higher age (OR: 1.05 per increasing year; 95% CI: 1.01–1.09) and BMI (OR: 1.05 per increasing point BMI; 95% CI: 1.01–1.10) were both independently associated with the occurrence of major complications, adjusted for surgical technique (TLH or TAH) (Table 2).

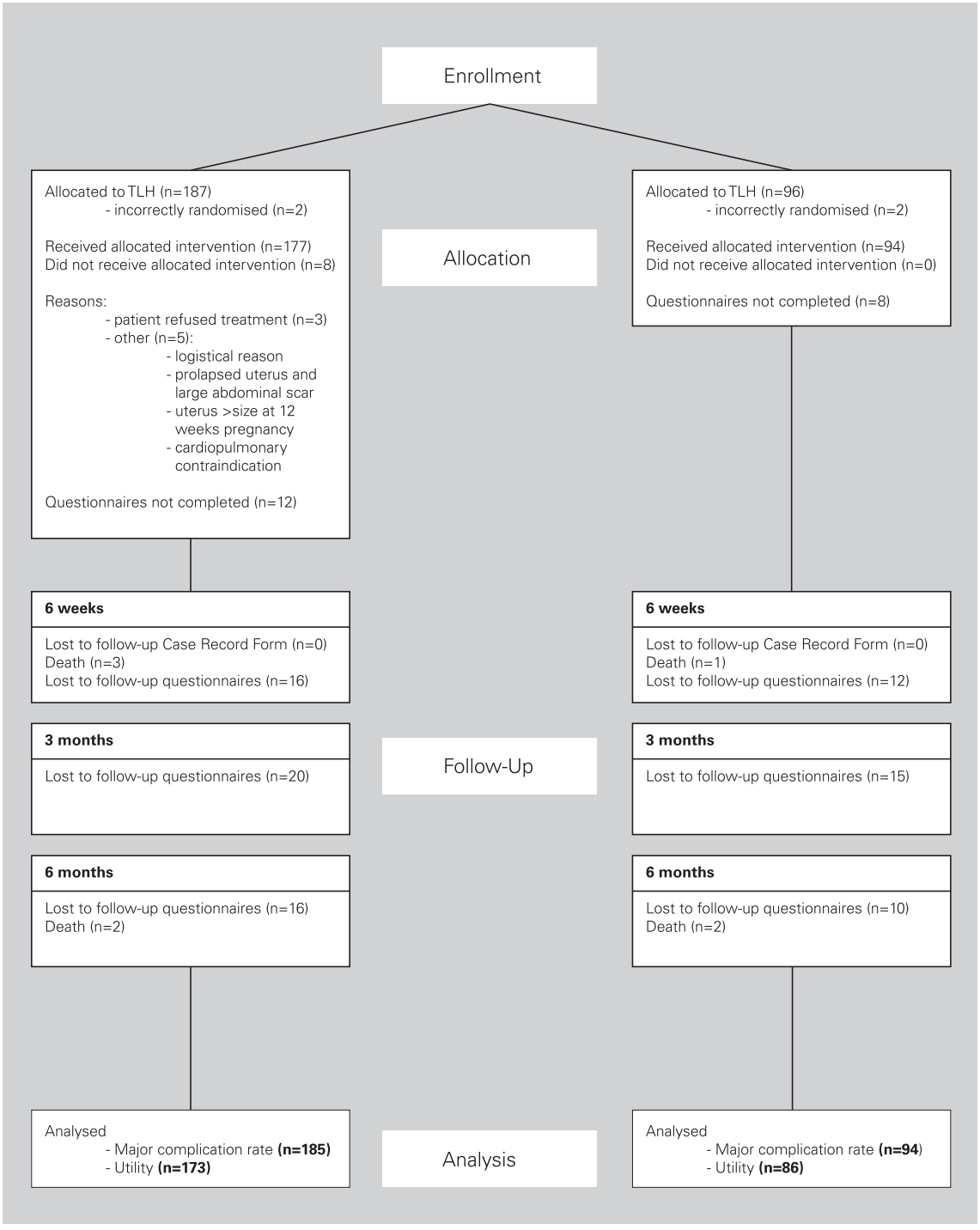

Fig. 1 – Flowchart of patients.

Conversions to laparotomy occurred in 20 (10.8%) of all laparoscopy patients. Both higher BMI (OR: 1.17 per increasing point kg/m^2; 95% CI: 1.09–1.25) and having had a previous laparotomy (OR: 3.45; 95% CI: 1.19–10.04) were independent predictors of the occurrence of a conversion (Table 2).

Based on the independent predictors of the effect measures, the following subgroups were constructed for the cost effectiveness analysis; (1) patients over 70 years of age (n = 61; TLH = 38, TAH = 23) and (2) patients with a BMI over 35 kg/m^2 (n = 55; TLH = 31, TAH = 24) (Fig. 2).

3.3. *Health outcome measures in elder or obese patients*

The major complication rate in patients over 70 years of age was 28.9% (11/38) in the TLH group versus 21.7% (5/23) in the TAH group. The major complication rate in patients with a BMI over 35 kg/m^2 was 25.8% (8/31) in the TLH group versus 25.0% (6/24) in the TAH group. Types of major complications for both subgroups are specified in Table 3.

The conversion rate in patients over 70 years of age was 10.5% (4/38) versus 10.9% (16/147) in the younger patients (p = 1.00). The conversion rate in patients with a BMI over 35 kg/m^2 was 32.3% (10/31) versus 6.5% (10/153) in the thinner patients ($p < 0.001$) (not in table). As Fig. 2 demonstrates, the estimated risk of conversion from laparoscopy to laparotomy increases with increased BMI, with in this study a steep rise in case of patients with a BMI >35 kg/m^2.

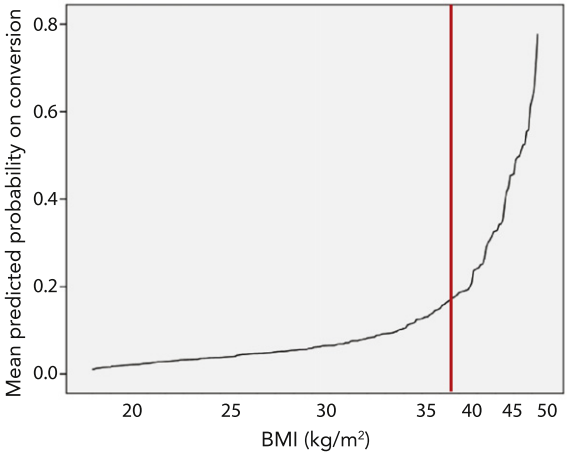

Fig. 2 – Probability of conversion to laparotomy based on body mass index (BMI).

Table 3 – Major complication and types of major complication per subgroup.

	N (%)[a]					
	Overall (N = 279)		Age >70 years (N = 61)		BMI >35 kg/m^2 (N = 55)	
	TLH (N = 185)	TAH (N = 94)	TLH (N = 38)	TAH (N = 23)	TLH (N = 31)	TAH (N = 24)
Patients with major complications	27 (14.6)	14 (14.9) (p = 0.95)	11 (28.9)	5 (21.7) (p = 0.54)	8 (25.8)	6 (25.0) (p = 0.95)
Intra operatively	5 (2.7)	4 (4.3)	2 (5.3)	1 (4.3)	1 (3.2)	3 (12.5)
Postoperatively	22 (11.9)	10 (10.6)	9 (23.7)	4 (17.4)	7 (22.6)	3 (12.5)
Type of major complication[b]						
Bowel injury	4 (2.2)	2 (2.1)	2 (5.3)	1 (4.3)	2 (6.5)	2 (8.3)
Ureter injury	2 (1.1)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder injury	2 (1.1)	1 (1.1)	1 (2.6)	0 (0.0)	1 (3.2)	1 (4.2)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection >38.0 °C	4 (2.2)	3 (3.2)	2 (5.3)	1 (4.3)	2 (6.5)	1 (4.2)
Haematoma requiring intervention	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhage requiring intervention	6 (3.2)	2 (2.1)	1 (2.6)	1 (4.3)	2 (6.5)	0 (0.0)
Nerve damage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound dehiscence requiring intervention	2 (1.1)	3 (3.2)	1 (2.6)	1 (4.3)	2 (6.5)	2 (8.3)
Wound infection requiring intervention	3 (1.6)	1 (1.1)	0 (0.0)	1 (4.3)	1 (3.2)	1 (4.2)
Ileus requiring intervention	3 (1.6)	1 (1.1)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dead	3 (1.6)	1 (1.1)	3 (7.9)	1 (4.3)	0 (0.0)	0 (0.0)
Other major complications	3 (1.6)	2 (2.1)	2 (5.3)	1 (4.3)	1 (3.2)	0 (0.0)
Total	33 (17.8)	16 (17.0)	14 (36.8)	7 (30.4)	11 (35.5)	7 (29.2)

[a] Unless otherwise specified.
[b] Not tested because groups were too small for a significant difference.

3.4. *Cost effectiveness analysis in elder and obese patients*

In the total population, with a mean difference of €-6 (i.e. lower costs for TLH) in costs and a mean difference of 0.16% (less complications in TLH arm) in major complication-free rate, the ICER generated is €-37 for laparoscopy, based on the bootstrap simulations (TLH $n = 142$; TAH $n = 70$).

For patients over 70 years of age, the mean difference in costs for was €136 (i.e. higher costs for TLH) with a mean difference in major complication-free rate of 8.46% (i.e. less complications in TLH arm), generating an ICER of €16 for laparoscopy (TLH $n = 26$; TAH $n = 15$). From the bootstrapped cost effectiveness plane (Fig. 3A) it can be seen that the ICER is located at the North East quadrant. For patients with a BMI over 35 kg/m^2 subgroup, the mean difference in costs for the BMI subgroup was €-272 (i.e. lower costs for TLH), with a mean difference in major complication-free rate of −5.07% for laparoscopy (i.e. more complications in TLH arm), generating an ICER of €54 for TLH (TLH $n = 23$; TAH $n = 18$). This ICER is located in the South West quadrant of the cost effectiveness plane (Fig. 3B).

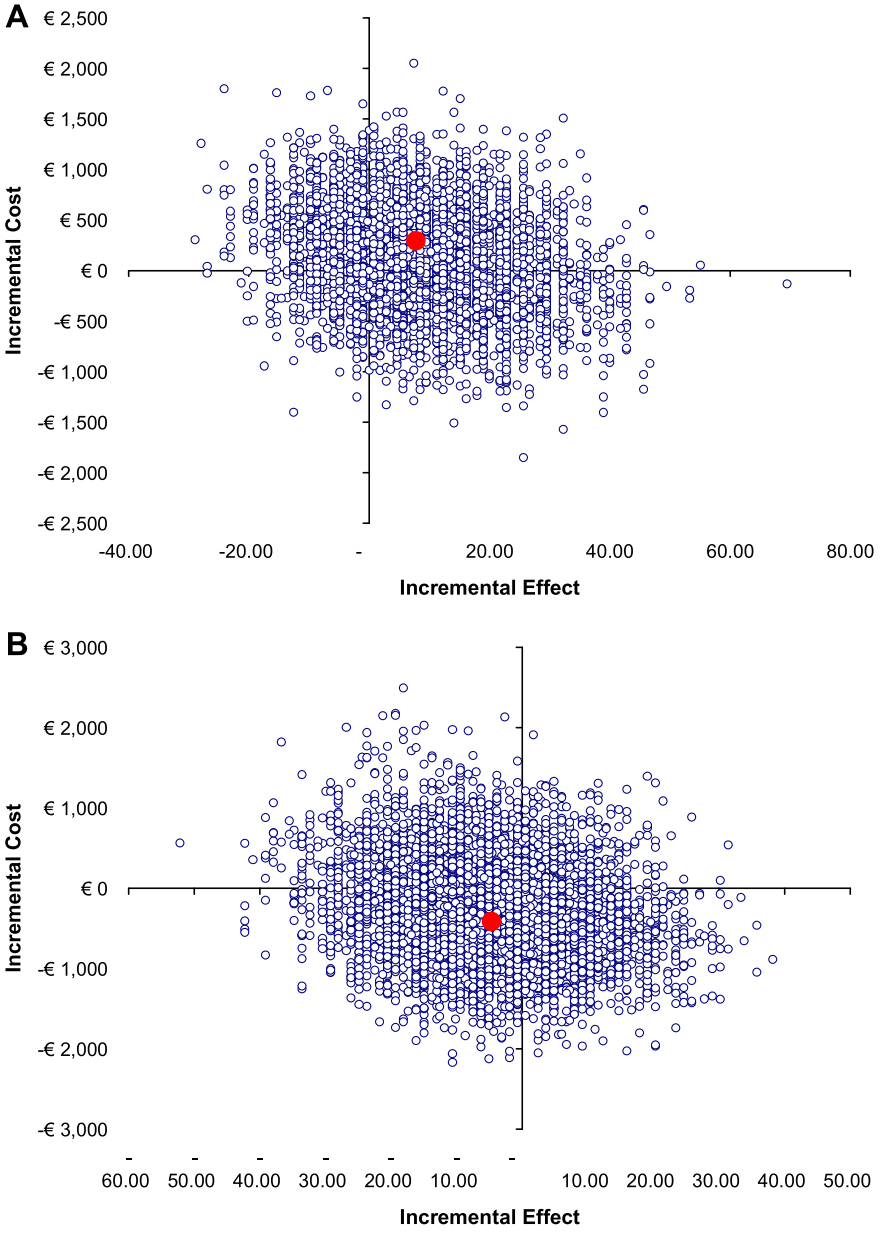

Fig. 3 – Cost effect planes in older and obese patients. (A) Incremental costs per additional major complication-free patient over 70 years of age. (B) Incremental costs per additional major complication-free patient with a BMI >35 kg/m^2. *Scatterplot of the estimated (joint density) of incremental costs and incremental effects of total abdominal hysterectomy (TAH) versus total laparoscopic hysterectomy (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 were 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.

4. Discussion

Our subgroup analysis based on the patient profile documents that elder and obese are at increased risk to develop major complications due to surgical treatment, either by TLH or TAH, of early stage endometrial cancer. Obese patients (BMI >35 kg/m^2) have a substantial higher conversion rate after laparoscopy compared to thinner patients. TLH is cost effective in patients over 70 years of age, but not in patients with a BMI >35 kg/m^2 based on major complication-free rate as primary measure of effect. In the latter, TLH is less costly with no additional effect compared to TAH meaning that TLH is by definition not cost effective in obese patients.

Our data showed that obesity is a predictor of higher major complication rates, irrespective of the surgical technique used (i.e. TAH or TLH). The major complication in obese patients treated by laparoscopy (25.8%: 10.4–41.2%) or laparotomy (25.0%: 7.7–42.3%) is comparable. In contrast with our results, in a retrospective single centre study comparing both surgical techniques in obese women with endometrial cancer, substantially more complications occurred after an abdominal approach (58.1%: 40.7–75.5%) when compared to laparoscopy (21.3%: 9.6–33.0%).[18] Furthermore, another study showed that endometrial cancer in severely obese can be managed safely by laparoscopy. Neither the conversion rate, nor the complication rate was higher for this specific group.[22]

Our study indicated that age is a predictor of the occurrence of major complications, though the major complication rates for laparoscopy (28.9%: 14.5–43.3%) and laparotomy (21.7%: 4.9–38.5%) are comparable. In a retrospective series of Scribner et al. in elder women with endometrial cancer, fewer complications were observed in the laparoscopy group (26.9%: 16.3–37.5%) than in the laparotomy group (62.2%: 48.0–76.4%).[19] However, due to the retrospective and non-randomised design of these studies, they are prone to selection and information bias. A small randomised single centre trial in endometrial cancer ($n = 122$) indicated that in a subgroup of obese, elder patients with co-morbidity, surgical technique was the only independent predictor of complications in favour of laparoscopy, which is not in agreement with our results as shown in Table 2.[20]

Our results indicate that the probability of a conversion increases with higher BMI. In patients with a BMI over 35 kg/m^2, 32.3% of all laparoscopic procedures were converted to a laparotomy. Consistent with our finding, a large multi-institutional randomised trial (GOG2222) in clinical stage I and IIA endometrial cancer patients showed that the risk of conversion was higher with higher BMI, but also with higher age and metastatic disease.[23] The fact that metastatic disease was not related to conversion in our study might be because of the fact that we included only clinical stage I patients and hence advanced disease was very rare (3.0%). In the GOG2222 study, a lymphadenectomy was performed as part of the standard surgical treatment in both arms, which makes the surgical procedure more advanced, complex and prolonged, and therefore might lead to higher conversion and complication rates.

To our knowledge, this is the first analysis based on patient profiles from a rigorously setup randomised study comparing safety and cost effectiveness in early stage endometrial cancer patients. Despite the fact that the present analyses were performed in relatively small subgroups of obese and elder women, the result of this study can be used by clinicians and patients in decision making and might result in maximal health gain for patients, surgeons and policy makers. There is no evidence of benefit observed in terms of major complications in the subgroups between TLH and TAH. TLH is cost effective in patients over 70 years of age, but not in patients with a BMI over 35 kg/m^2, based on major complication-free rate as primary measure of effect. In general, TLH should be recommended as the standard surgical procedure in early stage endometrial cancer. In obese patients with a BMI >35 kg/m^2 TLH is not cost effective because of the high conversion rate. A careful consideration of laparoscopic treatment is needed for this subgroup. Surgeon experience level may influence this choice.

Conflict of interest statement

None declared.

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The sponsor (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.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *Cancer J Clin* 2009;**59**(4):225–49.
2. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early stage endometrial cancer: a randomised trial. *Lancet Oncol* 2010;**11**:763–71.
3. Parrazzini F, Negri E, La Vecchia C, et al. Role of reproductive factors on the risk of endometrial cancer. *Int J Cancer* 1998;**76**(6):784–6.
4. Park SL, Goodman MT, Zhang ZF, et al. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. *Int J Cancer* 2010;**126**(2):490–9.
5. Olsson JH, Ellstrom M, Hahlin M. Cost effectiveness and health status after laparoscopic and abdominal hysterectomy. *J Am Assoc Gynecol Laparosc* 1996;**3**:S37.

6. Perino A, Cucinella G, Venezia R, Castelli A, Cittadini E. Total laparoscopic hysterectomy versus total abdominal hysterectomy: an assessment of the learning curve in a prospective randomized study. *Hum Reprod* 1999;**14**:2996–9.
7. Garry R, Fountain J, Mason S, et al. The evaluate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. *BMJ* 2004;**328**:129.
8. Marana R, Busacca M, Zupi E, et al. Laparoscopically assisted vaginal hysterectomy versus total abdominal hysterectomy: a prospective, randomized, multicenter study. *Am J Obstet Gynecol* 1999;**180**:270–5.
9. Persson P, Wijma K, Hammar M, Kjolhede P. Psychological wellbeing after laparoscopic and abdominal hysterectomy – a randomised controlled multicentre study. *Br J Obstet Gynaecol* 2006;**113**:1023–30.
10. Kluivers KB, Hendriks JC, Mol BW, et al. Quality of life and surgical outcome after total laparoscopic hysterectomy versus total abdominal hysterectomy for benign disease: a randomized, controlled trial. *J Minim Invasive Gynecol* 2007;**14**:145–52.
11. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. *Gynecol Oncol* 2009;**112**:126–33.
12. Malur S, Possover M, Michels W, Schneider A. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer – a prospective randomized trial. *Gynecol Oncol* 2001;**80**(2):239–44.
13. Fram KM. Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. *Int J Gynecol Cancer* 2002;**12**:57–61.
14. Zorlu CG, Simsek T, Ari ES. Laparoscopy or laparotomy for the management of endometrial cancer. *JSLS* 2005;**9**:442–6.
15. Zullo F, Palomba S, Russo T, et al. A prospective randomized comparison between laparoscopic and laparotomic approaches in women with early stage endometrial cancer: a focus on the quality of life. *Am J Obstet Gynecol* 2005;**193**:1344–52.
16. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol* 2009;**27**:5337–42.
17. Bijen CB, Vermeulen KM, Mourits MJ, et al. Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: a randomised trial. *Gyn Oncol* 2011;**121**(1):76–82.
18. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy versus total abdominal hysterectomy for obese women with endometrial cancer. *Int J Gynecol Cancer* 2005;**15**(2):319–24.
19. Scribner Jr DR, Walker JL, Johnson GA, et al. Surgical management of early-stage endometrial cancer in the elderly: is laparoscopy feasible? *Gynecol Oncol* 2001;**83**(3):563–8.
20. Tozzi R, Malur S, Koehler C, Schneider A. Analysis of morbidity in patients with endometrial cancer: is there a commitment to offer laparoscopy? *Gynecol Oncol* 2005;**97**(1):4–9.
21. Bijen CB, Briet JM, de Bock GH, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy in the treatment of patients with early stage endometrial cancer: a randomized multi center study. *BMC Cancer* 2009;**9**:23.
22. Santi A, Kuhn A, Gyr T, et al. Laparoscopy or laparotomy? A comparison of 240 patients with early-stage endometrial cancer. *Surg Endosc* 2010;**24**:939–43.
23. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. *J Clin Oncol* 2009;**27**(32):5331–6.