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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

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HIGHLIGHTS

- Despite additional costs laparoscopy does not increase overall health care costs.
- Laparoscopy does not influence quality of life for patients with EOC.
- Laparoscopy prevents futile laparotomies with >1 cm residual disease.

ARTICLE INFO

ABSTRACT

Objective. To evaluate the cost-effectiveness of a diagnostic laparoscopy prior to primary cytoreductive surgery to prevent futile primary cytoreductive surgery (i.e. leaving >1 cm residual disease) in patients suspected of advanced stage ovarian cancer.

Methods. An economic analysis was conducted alongside a randomized controlled trial in which patients suspected of advanced stage ovarian cancer who qualified for primary cytoreductive surgery were randomized to either laparoscopy or primary cytoreductive surgery. Direct medical costs from a health care perspective over a 6-month time horizon were analyzed. Health outcomes were expressed in quality-adjusted life-years (QALYs) and utility was based on patient's response to the EQ-5D questionnaires. We primarily focused on direct medical costs based on Dutch standard prices.

Results. We studied 201 patients, of whom 102 were randomized to laparoscopy and 99 to primary cytoreductive surgery. No significant difference in QALYs (utility = 0.01; 95% CI 0.006 to 0.02) was observed. Laparoscopy reduced the number of futile laparotomies from 39% to 10%, while its costs were € 1400 per

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intervention, making the overall costs of both strategies comparable (difference € − 80 per patient (95% CI − 470 to 300)). Findings were consistent across various sensitivity analyses.

Conclusion. In patients with suspected advanced stage ovarian cancer, a diagnostic laparoscopy reduced the number of futile laparotomies, without increasing total direct medical health care costs, or adversely affecting complications or quality of life.

1. Introduction

Epithelial ovarian cancer is the seventh most common cancer in women worldwide [1]. More than 75% of patients are diagnosed with advanced stage disease and five-year survival rates range between 30 and 50%. Standard treatment consists of primary cytoreductive surgery (PCS) followed by platinum-based chemotherapy [2]. PCS is recommended when there is a high likelihood of achieving cytoreduction to no visible disease or <1 cm residual disease. There is an active discussion on which patients should undergo PCS and who should start with neo-adjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) [2]. Two randomized clinical trials showed non-inferiority of treatment comparing NACT with ICS versus PCS in patients with FIGO stage IIIC-IV, two trials are ongoing [3–6].

The need to address the ideal timing of cytoreduction is of great clinical importance. PCS resulting in no residual disease results in the best survival, but requires extensive surgery with a subsequent higher risk of morbidity [7]. If extensive disease is present at primary surgery and cytoreductive surgery to no residual disease or <1 cm seems not possible, NACT with ICS is considered a good alternative treatment strategy [8]. This would require the identification of patients with extensive disease who are likely to have >1 cm residual tumor after PCS [9].

Current non-invasive diagnostic methods including physical examination, ultrasonography, abdominal computed tomography (CT), and serum tumor markers like CA125 and Carcinoembryonic antigen do not accurately predict completeness of surgery [10]. There is a need for more accurate prediction which seems possible with a diagnostic laparoscopy prior to surgery [11].

Recently, we described the results of a multicenter randomized clinical study (LapOvCa trial) where patients with suspected advanced ovarian cancer were randomized to undergo either PCS or a diagnostic laparoscopy to predict completeness of surgery. The laparoscopy was used to guide the decision to start with either PCS indeed or NACT. This study showed the benefits of a routine diagnostic laparoscopy before planned PCS, to identify those patients at risk of residual disease after surgery, and thereby prevent futile laparotomies with >1 cm residual disease [12]. In the group of patients randomized to diagnostic laparoscopy only 10% of the patients underwent a futile laparotomy with >1 cm residual disease versus 39% of the patients randomized for direct PCS.

As diagnostic laparoscopy is an invasive procedure, with a small risk of complications, and will incur additional costs, it is not clear whether the cost reduction from avoided surgeries makes up for the cost increase from the routine use of laparoscopy before surgery. In literature no cost analysis of diagnostic laparoscopy in ovarian cancer has been described. Some studies compare costs of PCS an NACT treatment with contradictory result, two studies showed higher costs for PCS treatment where one study showed lower costs for PCS treatment [13–15]. Furthermore, there are no studies investigating the influence of laparoscopy in the diagnostic work-up on quality of life (QOL). Greimel et al. describes similar QOL for either treatment with PCS of treatment with NACT [16].

In this study we compared PCS versus diagnostic laparoscopy followed by PCS or NACT and we analyzed the costs and QOL over 6-months' time alongside a randomized clinical trial.

2. Methods

2.1. Economic evaluation

2.1.1. Design

An economic evaluation from a health care perspective with a 6-month time horizon was performed alongside a randomized clinical trial. A trial based "as opposed to model based" analysis was performed. We hypothesized that the introduction of a diagnostic laparoscopy could reduce the number of futile laparotomies (with >1 cm residual tumor), without impact on survival or long-term health outcomes. As we expect to prevent exposure of patients to this extensive surgery, thereby favorably affecting quality of life (QOL) during this period, we measured utility at three time points within this 6-month horizon.

Our study was reported according to the CHEERS guidelines [17]. Direct medical costs are associated with health care utilization related to diagnostic and surgical interventions, medical procedures and hospital admission days. Costs of chemotherapy treatment were not taken into account. Length of hospital admission was calculated from preoperative admittance, one day prior to cytoreductive surgery until the day of hospital discharge.

A cost analysis was undertaken to assess costs and effects of both treatment arms from a health care perspective. In the Netherlands the health care system is based on insured care and general unit costs were estimated by the Dutch guidelines for economic evaluation (College Voor Zorgverzekeringen, CVZ 2015). A 6-month time horizon was selected to represent costs associated with the initial treatment by laparoscopy and cytoreductive surgery (primary or interval cytoreductive surgery).

The cost analysis estimated the additional costs that needed to be invested when a diagnostic laparoscopy was performed before the PCS. All patients were analyzed on an intention-to-treat basis. A cost-utility analysis was undertaken to evaluate the balance between incremental costs and health gains (QALYs) of adding the laparoscopy. The incremental cost-effectiveness ratio is expressed as additional costs per QALY gained. Finally, cost effectiveness planes were constructed depicting 5000 bootstrap replications of the trial data. Analyses were performed using Microsoft Excel, SPSS software package, version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA), and R 3.1.3 using packages ICE infer for cost-effectiveness analysis and Amelia for multiple imputation.

2.2. Assessment of effects

Utilities to adjust for health-related quality of life were based on patients response to the Euroqol-5D (EQ-5D) questionnaire, measured at baseline, 3 months after start of treatment and after completion of initial treatment including chemotherapy (approximately 6 months). We calculated the QALYs per patient by measurement of the area under the linear interpolation of the three measuring moments. Utilities were calculated using the EQ-5D Index Calculator, which has been validated for the Dutch population [18]. Utilities at the three different measurements were subsequently used to calculate QALYs. Differences in utilities between treatment groups were tested using a Repeated Measures

ANOVA. P values of <0.05 were considered to indicate statistical significance (2-tailed test). Multiple imputations were used to impute missing EQ-5D data so that all patients could be included in the estimation of Incremental Cost Effectiveness Ratios (ICER).

To evaluate the impact on disease-specific QOL domains, validated questionnaires were assessed; the European Organization for Research and Treatment of Cancer (EORTC) QLQ C-30 (cancer specific) and OV-28 (ovarian cancer specific) [19]. The QLQ-C30 and OV-28 scales and single items were linearly transformed to 0–100 and analyzed according to the procedures recommended by the EORTC Quality of Life Group [20]. To avoid multiple testing a summary score of the QLQ C30 was calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global QOL scale and the Financial Impact scale are not included) [21]. Missing data were not imputed for the QLQ-C30 and the OV-28 questionnaires. Higher scores on the QLQC-30 functioning and the global QOL scale indicated better functioning or QOL, whereas higher scores on the symptom scales represented a higher level of symptoms. A clinically significant difference of at least 10 points was classified as improved or worsened on the EORTC QLQ-C30 [22]. Mean scores and standard deviations were calculated for the multi-item and single-item scales. The clinical relevant differences between the treatment arms for QOL scores were analyzed by a Repeated Measures ANOVA.

2.3. Assessment of costs

Resource use data included procedure costs, hospital stay and costs within the postoperative period including complications and additional homecare (Table 1). All readmissions due to complications were registered. In-hospital medical procedures were assessed and patient questionnaires were used to collect information on use of additional home care, professional as well as informal. Information on outpatient visits was not available. To prevent bias by missing data, multiple imputation was used.

Group differences in resource use were tested by the unpaired t-test or Mann–Whitney U test, if data were not normally distributed. Resource use was multiplied by unit costs, and total costs per patient were estimated. Cost drivers were valued according to standard Dutch guidelines for economic evaluation (College Voor Zorgverzekeringen, CVZ 2015). The price level of 2014 was used and costs were calculated in Euros (€). Actual costs for the laparotomy and laparoscopy were estimated, informal care was valued by using shadow unit costs (Table 1). If laparoscopy and laparotomy were performed in one session, the 40% overhead costs of the laparoscopy were deducted.

2.4. Sensitivity analysis

The following univariate sensitivity analyses were performed to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis. The first sensitivity analysis was conducted to assess how differential costs would have changed if laparoscopy was always performed in one session with the cytoreductive surgery, in case primary surgery was feasible. A second sensitivity analysis calculated the costs if laparoscopy and laparotomy were performed in a subsequent session, by neglecting the reduction of € 320 for patients where laparoscopy and laparotomies were conducted in one session. A third sensitivity analysis calculated extra

Table 1
Actual resource use and mean difference in costs per patient within LapOvCa trial (2014 Euros).

Direct medical costs				Laparoscopy before surgery (n = 102)			Primary surgery (n = 99)			
Care	Unit	Unit costs	Method	Number of patients receiving care n (%)	Mean use of care for all patients (SD)	Mean costs per patient (SD)	Number of patients receiving care n (%)	Mean use of care for all patients (SD)	Mean costs per patient (SD)	Mean difference in costs[a]
Surgery										
Laparoscopy[b]	per surgery	€ 1400	Cost price	100 (98%)	0.98 (0.14)	€ 1373 (195)	1 (1%)	0.01 (0.10)	€ 14 (140)	€ 1358
Laparotomy[b]	per surgery	€ 2250	Cost price	102 (100%)	1.0 (0.28)	€ 2250 (633)	99 (100%)	1.24 (0.45)	€ 2795 (1021)	€ −545
No laparotomy		€ 0		4 (4%)			1 (1%)			
1 laparotomy		€ 2250		94 (92%)			73 (74%)			
2 laparotomy		€ 4500		4 (4%)			25 (25%)			
Hospital stay										
IC admission	per day	€ 1186	CVZ 2015	9 (9%)	0.18 (0.80)	€ 209 (950)	12 (12%)	0.16 (0.47)	€ 192 (554)	€ 18
ward admission	per day	€ 642	CVZ 2015	102 (100%)	9.2 (5.33)	€ 5923 (3420)	99 (100%)	10.25 (8.32)	€ 6582 (5344)	€ −659
Additive diagnostic tests										
MRI scan	per investigation	€ 215	CVZ 2015	0			0			€ 0
CT scan	per investigation	€ 140	CVZ 2015	9 (9%)	0.12 (0.43)	€ 16 (60)	10 (10%)	0.14 (0.52)	€ 20 (72)	€ −3
Ultrasound	per investigation	€ 80	CVZ 2015	6 (6%)	0.07 (0.29)	€ 6 (23)	4 (4%)	0.06 (0.34)	€ 5 (28)	€ 1
Complications										
Extra ward admission	per day	€ 642	CVZ 2015	10 (10%)	1.10 (4.71)	€ 705 (3032)	10 (10%)	1.08 (5.32)	€ 694 (3418)	€ 11
Blood products	per Packet Cell	€ 216	CVZ 2015	13 (13%)	0.44 (1.53)	€ 95 (331)	10 (10%)	0.30 (1.13)	€ 65 (244)	€ 30
Extra surgical intervention	per minute surgery	€ 10	Cost price	7 (7%)	7.47 (29.46)	€ 75 (295)	4 (4%)	3.61 (21.43)	€ 36 (2174)	€ 39
Additional homecare										
Formal homecare	per hour	€ 50	CVZ 2015	80 (78%)[c]	1.66 (3.51)	€ 83 (176)	74 (75%)[d]	3.17 (5.63)	€ 159 (282)	€ −75
Informal homecare	per hour	€ 14	CVZ 2015	80 (78%)[c]	9.71 (22.43)	€ 136 (314)	74 (75%)[d]	12.43 (22.18)	€ 174 (311)	€ −38
Total costs[e]						€ 9980 (4200)			€ 10,060 (5770)	€ −80

n = number of patients.
[a] Costs laparoscopy arm minus costs primary surgery arm.
[b] Overhead costs included.
[c] Data missing for 22 patients.
[d] Data missing for 25 patients.
[e] Based on cost-effectiveness analyses with imputed data for homecare and based on quality-adjusted life-years (QALYs).

costs for the empty theatre in case laparoscopy and laparotomy were planned in one session and the surgery was ceased after the laparoscopy, based on the estimation at laparoscopy of inoperable disease leaving >1 cm residual tumor. Costs for an empty theatre were estimated at € 1100. In clinical practice an empty theatre could be used to perform other surgeries, diminishing these costs, therefore this sensitivity analysis presents the 'worst case' scenario. A fourth and fifth sensitivity analysis investigated the effect of an increase and decrease of the costs of cytoreductive surgery.

2.5. Original trial design

Between May 2011 and February 2015 we performed a randomized controlled trial. A more detailed description of the LapOvCa trial can be found elsewhere [12]. In short, 201 patients suspected of advanced stage ovarian cancer who qualified for PCS were randomized to either diagnostic laparoscopy (n = 102) or primary cytoreductive surgery (n = 99). In the laparoscopy group, the laparoscopy was used to guide treatment strategy: either PCS or NACT followed by ICS.

The trial showed a statistically significant decrease in futile laparotomies (PCS with >1 cm residual disease) in the laparoscopy group compared to the PCS group (10% versus 39%) (RR 0.25, 95% CI 0.13 to 0.47, p < 0.001). No differences in complication rate or survival were observed. In the laparoscopy group, 22 patients had a grade three or four adverse event during treatment including complications due to cytoreductive interval surgery (by the Common Terminology Criteria for Adverse Events) versus 26 in the primary surgery group (RR 0.82, 95% CI 0.50 to 1.35, p = 0.44) Only one complication was direct related to laparoscopy (more details in the primary article [12]). The median overall survival was comparable between both groups (44.4 months (IQR: 16.8–> 55)) in the laparoscopy versus 46.3 months (IQR: 13.9–52.6) in the PCS group (p = 0.94), respectively, Hazard ratio 1.33 (95% CI 0.89 to 1.98).

2.6. Received surgical interventions

In the laparoscopy group, 63/102 patients (62%) underwent PCS; and 39/102 patients received NACT followed by ICS. Fig. 1 shows the

design and number of patients undergoing the different treatment strategies. For 52/62 patients who received laparoscopy and PCS, both surgeries were performed in one session, while in 10/62 patients laparoscopy and PCS were performed in two subsequent sessions. For the 39 patients assigned to NACT, laparoscopy and surgery were performed in multiple sessions. In the group randomized for PCS 93/99 patients (94%) underwent PCS. Six patients had deterioration of their physical condition after randomization and were unfit for surgery; therefore they received NACT.

3. Results

3.1. Study population

We studied 201 patients, of whom 102 were randomized to laparoscopy and 99 to PCS. Of all patients data was available on the performed surgeries, hospital stay, additive diagnostic tests and complications. Data of additional homecare and QOL was gathered by questionnaires, with missing values due to non-responders. Response rates to the questionnaires were 73% at baseline, 57% during treatment and 53% at the end of treatment. No significant differences in response rates were observed between both treatment arms. In total, 12 patients died within 6 months after randomization (6 in each treatment arm), QOL after completion of treatment was scored zero for these patients. For the non-responders data was imputed for the EQ-5D scores and the use of homecare. When comparing baseline characteristics of responders (n = 146) to questionnaires with non-responders (n = 55), most characteristics where comparable between treatment groups. Except for WHO performance status, more non-responders had WHO score 0, and two out of eight treatment centers had significantly lower response rates of the questionnaires.

3.2. Costs and cost-effectiveness analyses

The cost drivers used for the cost analyses with accompanying quantity units are depicted in Table 1. Most care was comparable for both groups, except for laparoscopies and number of laparotomies (in the
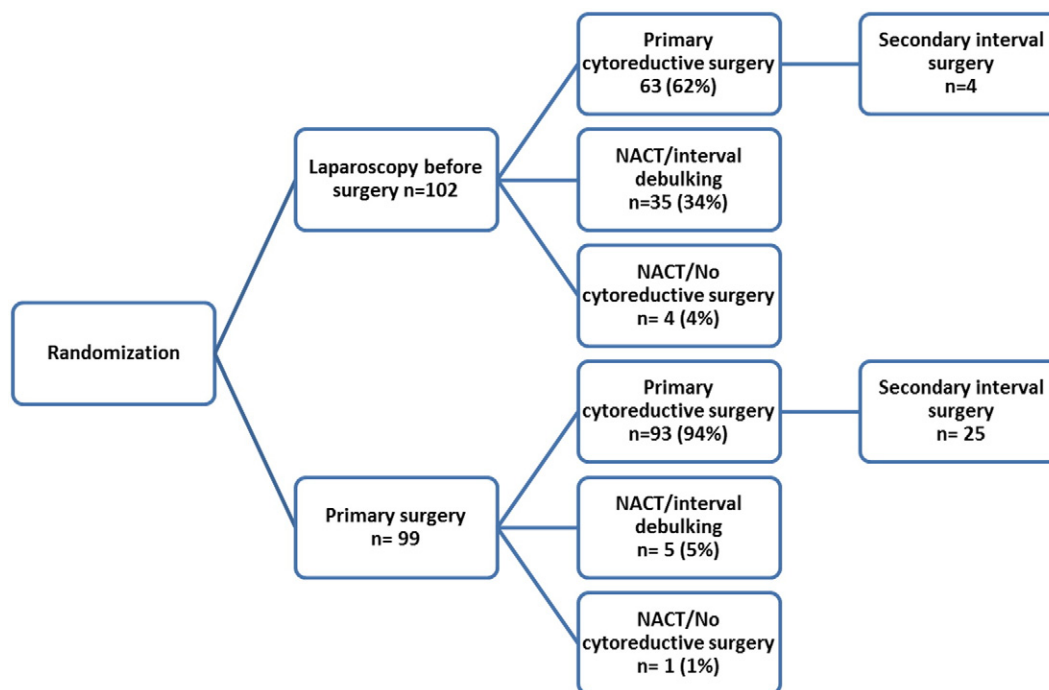

Fig. 1. Sequence of surgeries in both treatment arms; patients who had laparoscopy before surgery versus the group of patients who underwent primary surgery. NACT, Neoadjuvant chemotherapy.

laparoscopy group 4 patients received two laparotomies compared to 25 patients in the PCS group) and informal homecare (mean of 9 h and 43 min in the laparoscopy group and 12 h and 26 min in the PCS group).

Mean costs per patient were € 9980 (SD: € 4200) in the laparoscopy group compared to € 10,060 (SD: € 5770) in the PCS group. The mean cost reduction was € −80 (95% CI −470 to 300) per patient and an observed effectiveness difference of 0.01 (95% CI 0.006 to 0.02) in QALYs in favor of the laparoscopy group. This generates an ICER of € −8000 per QALY gained in favor of the laparoscopy group based on the bootstrapped simulations (Fig. 2a), indicating that treatment of 100 patients result in gain of 1 QALY and a cost reduction of € 8000. The probability that adding a laparoscopy is considered cost-effective when increasing the willingness to pay threshold, is visualized in cost-effectiveness acceptability curve (Fig. 2b). At willingness to pay threshold of € 20,000 there is an 82% change of being cost-effective.

3.3. Health-related quality of life

Quality of life was not different for both treatment arms over the different time frames (EQ-5D time trade-off (TTO) scores p = 0.82 and EQ-5D visual analogue scale (VAS) scores p = 0.65, Table 2).

3.4. Disease-specific quality of life domains

No clinical relevant (>10 points) or statistical significant differences were seen, between the laparoscopy group and the PCS group for the QLQ C30 and the QLQ OV28 functioning or symptoms scales (Supplementary Table S1 and S2). Both treatment arms showed improvement at the end of initial treatment compared to baseline values on all aspects of the EORTC QLQ C-30 questionnaires (Supplementary Table S1). Scores for pain and appetite loss improved most (decrease of >10 points, defined as clinically relevant).

We performed a post-hoc analysis considering all patients off both treatment arms, comparing patients with a futile laparotomy (with >1 cm residual disease after PCS) to patients without a futile laparotomy. This revealed clinical relevant differences of >10 points on some of the aspects of the EORTC QLQ C-30 and QLQ OV28 questionnaire (Supplementary Table S3 and S4); the summary score was lower for the patients with a futile laparotomy (p = 0.05). Patients with a futile laparotomy showed a worse score on at least 2 time points on; role function (limited in doing either your work, hobbies or other daily or leisure activities) (p = 0.01), fatigue (p = 0.02), pain (not statistical significant, p = 0.09) and burden of the disease (attitude to disease and treatment, not statistical significant, p = 0.09).

3.5. Sensitivity analysis

Five sensitivity analyses were performed, varying different cost scenarios. The first sensitivity analysis calculates the scenario when laparoscopy and PCS are always performed in one session. A subtraction of € 320 was calculated for all patients receiving laparoscopy and continuing with PCS (62%). This model has a cost difference of € −120 (95% CI −500 to 270) per patient in favor of the laparoscopy group. Second sensitivity analysis illustrates the costs if laparoscopy and laparotomy were always performed in separate sessions; higher costs for the laparoscopy, by including 40% overhead costs for all laparoscopies. This model results in a difference of costs of € 80 (95% CI −310 to 500) per patient, reflecting minimal extra costs for the laparoscopy group. The third sensitivity analysis accounts an extra fee of € 1100 for an empty surgery theatre in case the surgery is ceased after the laparoscopy when laparoscopy and cytoreductive surgery are performed in one session, this occurred in 38% of patients. This showed a mean difference in costs of € 280 (95% CI −100 to 670) per patient, in favor of the PCS group. In the fourth and fifth sensitivity analyses, we increased and decreased costs for cytoreductive surgery with a half standard deviation of the costs for a cytoreductive surgery (€ 630,-). This resulted in a cost difference of € −250 (95% CI −650 to 140) per patient, in favor of the laparoscopy group when the unit cost of the cytoreductive surgery was increased to € 2880, or a minimal cost difference of € 85 (95% CI
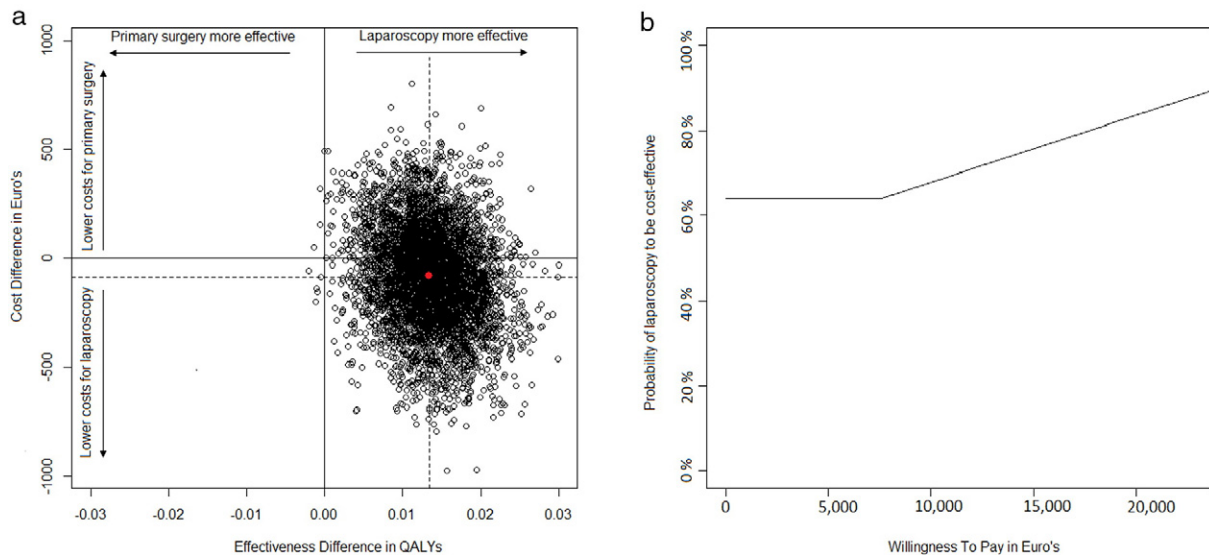

Fig. 2. Incremental Cost Effectiveness Ratios (ICER) of the main analysis and acceptability curve. a. ICER, cost difference in Euros and effectiveness difference in quality-adjusted life-years. * = scatterplot of the estimated (joint density) of incremental costs and incremental effects of laparoscopy versus primary surgery, 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. Dots in the two quadrants right from the Y axis represent the replications were laparoscopy is more effective than primary surgery, and vice versa for the quadrants left from the Y axis. Dots in the two quadrants below the X axis represent lower costs of laparoscopy versus primary surgery and vice versa for dots in the quadrants above the X axis. b. Cost-effectiveness acceptability curve (CEAC) of laparoscopy to being cost effective. The CEAC shows that for lower values of willingness to pay for a QALY, laparoscopy has a 63% probability of being cost-effective. When the willingness to pay increases to 20,000 euros per QALY, this probability increases to 82%.

Table 2
EQ-5D time trade-off score and EQ-5D visual analogue scale per treatment group.

EQ-5D	Laparoscopy before surgery (n = 102)			Primary surgery (n = 99)			Significant difference
	Baseline, mean, (SD) n = 77	During treatment, mean, (SD) n = 57	End of treatment, mean, (SD) n = 52	Baseline, mean, (SD) n = 69	During treatment, mean, (SD) n = 57	End of treatment, mean, (SD) n = 55	
EQ-5D TTO score[a]	0.69 (0.24) n = 76	0.72 (0.27) n = 54	0.71 (0.29) n = 57	0.63 (0.26) n = 69	0.69 (0.21) n = 59	0.69 (0.26) n = 61	p = 0.82
EQ-5D VAS score	64.3 (18.5) n = 73	66.0 (16.6) n = 54	72.2 (14.2) n = 51	55.3 (22.8) n = 67	67.0 (13.9) n = 55	69.7 (14.3) n = 53	p = 0.65

[a] If patients died during treatment or before the end of treatment a score of 0 was assigned for the EQ-5D TTO score.

−290 to 460) per patient in favor of the primary surgery group when the unit cost of the cytoreductive surgery was decreased to € 1620. All different models are presented in Table 3, with mean costs per patients presented per randomization arm; figures of the ICERs are presented in Fig. 3.

4. Discussion

In this study we found that the use of laparoscopy in the diagnostic work-up for patients suspected of advanced stage ovarian cancer did not lead to additional costs. By avoiding futile laparotomies, laparoscopy costs were compensated. The use of laparoscopy had some positive influence on quality of life, when comparing patients with a futile PCS (with >1 cm residual tumor) to patients with no futile PCS. However, these differences did not lead to a significant difference between treatment arms for laparoscopy of PCS. Diagnostic laparoscopy can guide treatment selection for PCS or NACT, hereby preventing futile laparotomies, with >1 cm residual tumor, without increasing overall health care costs.

Since laparoscopy has a positive influence on reducing the number of futile laparotomies, but showed no gain in survival we performed a cost analysis to evaluate the costs and QOL for all patients. With this study we aimed to further guide diagnostic work-up to aid in treatment selection for primary surgery or NACT in patients suspected of advanced stage ovarian cancer. A recent published guideline of the American Society of Clinical Oncology underlines the discussion and difficulties of treatment selection, and recommends to perform primary surgery if this can result in <1 cm residual disease and otherwise to start with NACT [2]. Several retrospective and prospective case series described a diagnostic laparoscopy to be a reliable tool to identify patients suitable for PCS [23,24]. This is consistent with the findings and conclusion of our recent randomized controlled trial investigating the addition of laparoscopy; laparoscopy can guide the selection of patients suitable for primary surgery without increasing complications [12].

Our study is based on data of a multicenter randomized controlled trial enabling prospective registration of all resource use and a valid data collection [12]. Importantly, randomized controlled trials are the most rigorous way of determining the cost effectiveness of a treatment avoiding all sorts of bias [25]. Furthermore, the study population was representative for the Dutch population, since all Dutch gynecological oncology centers participated in this trial, strengthening the validity of our results. Nevertheless, the trial-based economic analysis was performed within the Dutch health care system.

Since the costs only vary minimally within the sensitivity analyses, we expect similar costs for the introduction of laparoscopy in different clinical practices or countries. Variation of laparoscopy costs influenced our results minimally, showing the least costs if laparoscopy and laparotomy are combined in one setting. However, if we correct for an empty theatre the costs are increased with extra costs for the laparoscopy group of € 280 per patient. In practice, the empty theatre would be used most of the time to perform other (emergency) surgeries, reducing these costs. The influences of the variable costs for laparotomies were in favor of the laparoscopy group. All cost variations remained below € 300 per patient, reflecting a low risk for extra costs when laparoscopy is added in the diagnostic process. To illustrate the financial benefit per patient of preventing a futile laparotomy (with >1 cm residual tumor), we compared the costs of patients with one laparotomy to patients with two laparotomies; showing a costs reduction of € 7940 when only one laparotomy was performed.

Despite the prospective registration of resource use, it is difficult to obtain a complete image of all costs. We had no information on medication during admission and we only calculated an average cost for admission in the ward or intensive care unit. Details of chemotherapy treatments or associated admissions were not documented. Neither were details of outpatient visits or hospice care. However, we do not believe that this affected our main conclusion, as these errors should affect both treatment arms, since the laparoscopy did not influence the number of chemotherapy cycles, complication rate or survival. Nevertheless, excluding these factors underestimates the total costs for these patients, clarifying our lower total costs compared to the total costs of PCS treatment in literature [13]. Data on homecare were incomplete, since these were collected by questionnaires leading to 27%- 47% of missing values. To prevent exclusion of data we used multiple imputation, hereby no data were lost and good price estimates could be made.

We evaluated the costs and QOL over a 6-month time horizon, since laparoscopy would be most influential on the treatment which takes place within 6 months and QOL data were available for this timeframe. No difference in survival was observed and we confirmed that

Table 3
Results of the sensitivity analysis, by treatment arm, costs are euros of reference year 2014.

| Model	Laparoscopy before surgery (n = 102)	Primary surgery (n = 99)	Mean difference in costs (95%CI)
	Mean costs per patient (SD)	Mean costs per patient (SD)	
Base case scenario	€ 9980 (4200)	€ 10,060 (5770)	€ −80 (−470 to 300)
Lower costs laparoscopy (€ 1080 vs € 1400) discount for combining laparoscopy and primary debulking	€ 9950 (4180)	€ 10,060 (5770)	€ −120 (−500 to 270)
Higher costs laparoscopy, no discount for combining laparoscopy and primary debulking	€ 10,140 (4160)	€ 10,060 (5770)	€ 80 (−310 to 500)
Taking empty theatre into account (€ 1100 extra if surgery was ceased after laparoscopy)	€ 10,360 (4300)	€ 10,070 (5780)	€ 280 (−100 to 670)
Higher costs laparotomy (€ 2880 vs € 2250)	€ 10,610 (4290)	€ 10,840 (5880)	€ −240 (−630 to 150)
Lower costs laparotomy (€ 1620 vs € 2250)	€ 9350 (4110)	€ 9280 (5670)	€ 70 (−310 to 440)
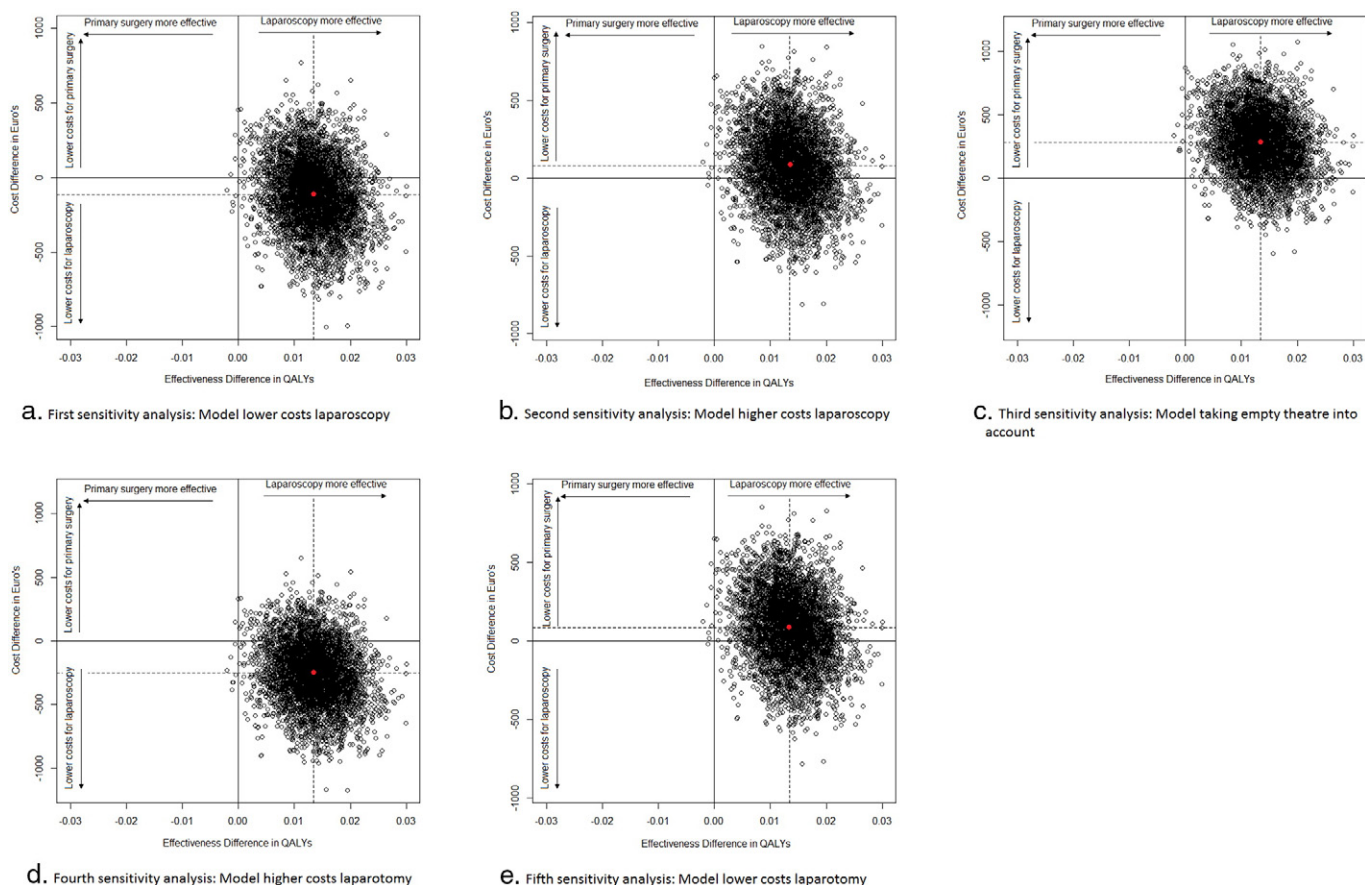
Fig. 3. Incremental Cost Effectiveness Ratios (ICER) of all models, cost difference in Euros and effectiveness difference in quality-adjusted life-years (QALYs). a. First sensitivity analysis: Model lower costs laparoscopy. b. Second sensitivity analysis: Model higher costs laparoscopy. c. Third sensitivity analysis: Model taking empty theatre into account d. Fourth sensitivity analysis: Model higher costs laparotomy. e. Fifth sensitivity analysis: Model lower costs laparotomy.

laparoscopy did not have a negative impact on QOL. Productivity losses were not included in the economic evaluation, based on the composition of the patient group characterized by patients with a mean age of 64 years.

When looking at quality of life, no significant differences were found between treatment arms. However, the impact of this severe disease on QOL might be greater than the impact of the respective surgical treatment modalities. On the other hand, considering all patients from both treatment arms, patients undergoing a futile laparotomy, with >1 cm residual disease at PCS, reported a worse QOL compared to those patients who underwent a successful PCS or received NACT.

In summary we performed a cost analysis alongside a randomized controlled trial, to prevent futile laparotomies by the introduction of a diagnostic laparoscopy in patients suspected of advanced ovarian cancer to guide further treatment strategy. Since no significant addition of complications occurred in the laparoscopy arm and no difference in survival was observed in the LapOvCa trial, treatment outcome, cost-effectiveness and QOL are important for the implementation of laparoscopy in daily practice. From this analysis, we conclude that laparoscopy is cost-neutral and reduces the number of futile laparotomies (i.e. leaving >1 cm residual disease). Therefore, we advocate the use of laparoscopy in the diagnostic work-up of patients suspected of advanced ovarian cancer, to guide treatment selection for either PCS or NACT.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.06.019.

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