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Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer

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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.

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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 neoadjuvant 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

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