

Master Thesis



**A Health Technology Assessment of
interval cytoreduction surgery with
hyperthermic intraperitoneal
chemotherapy in stage III Ovarian cancer.**

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A Health Technology Assessment of interval cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in stage III Ovarian cancer.

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Preface

In front of you is the report that is the product of my master thesis assignment for the study program Health Sciences at the University of Twente. This report is the result of research carried out for the Netherlands Cancer Institute in Amsterdam. First a general introduction is given to provide insight in the process I went through over the last couple of months. This is followed by the article which is the primary result of my research.

I would like to thank my supervisors Prof. Dr. van Harten and Dr. Retèl for their critical reviews and feedback. The weekly and monthly meetings helped me greatly to gain more insight in the subject at hand and to improve my research. Furthermore, I would like to thank Dr. W.J. van Driel, K. Sikorska and S. Koole for their help with understanding OV-HIPEC, the trial data and treatment protocols surrounding ovarian cancer.

During this project, I saw the endless passion that so many of the people working at the Netherlands Cancer Institute have. Every day they work hard trying to find new treatments, new diagnostic tools and new insights in the workings of cancer. For me this was a very inspiring environment to complete my master thesis in.

Lastly, I would like to thank my fellow students at the Netherlands Cancer Institute, I enjoyed our discussions and the coffee and lunch breaks. I appreciate the feedback and help you have given me to improve my research and my thesis. Finally, I would like to thank my family and friends for their support, not only during this thesis project but throughout my career as a student.

Chris van Lieshout

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List of Abbreviations

95%-CI	95% Confidence Interval
95%-CrI	95% Credible Interval
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CE plane	Cost Effectiveness Plane
CRS	Cytoreductive surgery
FIGO	International Federation for Gynecology and Obstetrics
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HRQoL	Health-Related Quality of Health
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IP	Intraperitoneal
IV	Intravenous
LY	Life Year
NKI	Netherlands Cancer Institute (<i>Nederlands Kanker Instituut</i>)
NZA	Dutch Healthcare Authority (<i>Nederlandse Zorg Autoriteit</i>)
OS	Overall Survival
OV-HIPEC	Ovarium Carcinoma – Hyperthermic Intraperitoneal Chemotherapy
PFS	Progression Free Survival
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
SD	Standard Deviation
SE	Standard Error
WTP	Willingness To Pay
ZIN	Dutch Healthcare Institute (<i>Zorginstituut Nederland</i>)

General Introduction

The aim of this thesis was to perform a Health Technology Assessment (HTA) of OV-HIPEC for women with ovarian cancer. In this general introduction to the article I will address the steps I have taken to complete my thesis and its context. First I will provide a short introduction of ovarian cancer and its treatment.

The majority of women diagnosed with ovarian cancer have an advanced stage cancer because there are no clear symptoms or reliable screening methods. The current treatment consists of surgery in which tumor load and peritoneal metastases are removed, primary cytoreductive surgery (CRS). In patients with suboptimal primary CRS or patients who require neo-adjuvant chemotherapy before surgery, interval cytoreductive surgery is performed. The majority of patients will have disease recurrence within 18 months. To improve survival, novel treatments are developed, one of which is OV-HIPEC. With this treatment, the abdominal cavity is perfused with hyperthermic chemotherapy right after surgery. To test this new treatment the Netherlands Cancer Institute (NKI) started a multicenter trial in 2004. During the trial patients were randomized to receive either regular interval CRS or interval CRS combined with OV-HIPEC to determine the effectiveness of OV-HIPEC compared to regular interval CRS.

The original aim of the assignment was to perform a cost effectiveness analysis (CEA) of OV-HIPEC for women with ovarian cancer. For a CEA, it is necessary to identify the relevant costs and the associated effects. The measure of effectiveness of OV-HIPEC was determined in the before mentioned trial. During the trial, participating patients fill out quality of life questionnaires at regular intervals. The plan was to use the results of these questionnaires to account for the quality of life during survival. In CEA's the additional costs of a treatment are divided by the additional life years gained, adjusted for the quality of life using utilities. Adjusting the life years gained with the quality of life during these years results in quality adjusted life year (QALY). The division of additional costs by additional QALY's results in the incremental cost effectiveness ratio (ICER) in euro/QALY.

To determine the cost effectiveness of a new treatment one needs to develop a model. In this model, a certain number of patients is simulated based on the results of the trial. In CEA's there are several different models one can use depending on the data available. Decision Tree's, Markov models and patient level modelling are some examples. At the start of the project the idea was, that since a trial was conducted and there was enough data available, to construct a patient level model in which patient characteristics are used to determine outcomes.

In subsequent weeks, it became apparent that although the number of patients included in the trial was enough to draw conclusions about the clinical effectiveness there were not enough patients to perform a patient level model. Therefore, it was decided to move forward with a Markov model. In a Markov model a certain number of patients move between pre-defined health states, in this case 1000

patients per treatment arm. The health states we defined in this study were; progression free survival (PFS), disease progression and death. The probability of a patient moving between these states was based on the PFS and overall survival (OS) probabilities found in the trial.

Since the trial was finished not long before this project started the statistician, still needed to do her analysis. Therefore, we started with identifying all actions performed to patients who were included at the NKI. This identification was done by asking the Business Intelligence team to retrieve all healthcare procedures and associated costs that were logged in the patients' medical files and medical bills. For the 82 patients for which this data was available this yielded in 28,000 lines of financial data related to treatment received.

To analyze the data all actions and treatments were categorized. After categorization, the principal investigator and resident physician, assisted in determining what usual care was and which actions and treatments needed to be included in this study. Connected to all these actions were internal tariffs, these tariffs do not represent the costs that are billed to the insurance companies. The overview of actions was used to identify what amount and type of care patients received. Other sources were used to identify the associated costs. Sources used in this study were the Dutch Healthcare Institute manual for standard prices and the Dutch Healthcare Authority maximum tariff list.

At this time, the costs of the healthcare received by patients in the two patient groups were determined. These costs were now used as input parameters in the model. As trial data became available and was entered the model it was now possible to simulate what happens to the patients, what care they receive and what costs are associated with the care received.

The trial also resulted in information about complications occurring during the treatment of patients. Together with the resident physician, we identified relevant complications and the complications that have the largest impact on the quality of life. The resident physician also provided input about what happens to patients when they move to the recurrence health state. The result of this was used as input for the model to determine the number and severity of complication for the patients modelled. At this time, the model was able to simulate what happens on a clinical level to patients during treatment and the subsequent five years whilst also providing the corresponding costs and effects.

Next the quality of life of patients needed to be added to the model. Quality of life data was gathered during the trial but unfortunately it was not possible to use this data for two reasons. First the data was not analyzed in time. The larger barrier was to transform the quality of life data to utilities used to determine QALY's. The questionnaires used do not directly result in utilities and therefore a mapping algorithm needs to be used. From a literature search it became apparent that there is no algorithm for ovarian cancer. The choice was made to use utility values from existing literature. Now that the quality of life is accounted for in the effects and since the costs of treatment was already determined the model is finished.

To account for the uncertainty surrounding some of the input parameters different distributions were used to make the model probabilistic. By performing a probabilistic sensitivity analysis (PSA) one

repeats the model 1000 times in a Monte Carlo simulation. The results of these iterations were plotted in a cost effectiveness plane. To identify the parameters with the largest impact on the cost effectiveness a sensitivity analysis was performed in which the mean of each parameter was altered with plus or minus 20 percent.

During the project, it became apparent that the results could be used to apply for provisional reimbursement under the Dutch health insurance law. If OV-HIPEC is to be reimbursed it should become available for all eligible patients. Since OV-HIPEC is a treatment that requires more operating room time and new facilities a nationwide implementation might have profound organizational implications. To assess these organizational aspects five surgeons, from different hospitals, who participated in the trial were approached for an interview. Four out of five agreed to be interviewed and their input was used to sketch the impact and context of this project in the discussion.

Over the past couple of months, I worked with great enthusiasm on this project. It was very interesting to see how diverse the field of Health Technology Assessment is. The data needed to perform a HTA was readily and plentiful available, this made the execution of the assignment seem straightforward. During the assignment, it became apparent that data is not always as useful as it may seem and that it might require a fair amount of work to prepare the data for use in the model. I found that there is somewhat of a mismatch between what you learn during courses on HTA and daily practice. This was especially true when it comes to data, in this case data was plentiful but it turned out that clinical practice is not always easy to model. During meetings with physicians they argued that care was delivered according to protocol but it is always possible to deviate from these protocols if patient characteristics and patient preference required this. For me it was hard to incorporate these exceptions in the model and therefore some hard choices and assumptions had to be made. In the end, I am pleased with the work I have done and pleased with the resulting article. I enjoyed my time at the NKI-AVL dearly and it was an experience I would not like to have missed.

Following this short general introduction explaining the steps I have taken to complete this thesis is the article I have written to report the results from my research. The article is titled; "*A Health Technology Assessment of interval cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in stage III Ovarian cancer*".

A Health Technology Assessment of interval cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in stage III Ovarian cancer.

C. van Lieshout.

Abstract

Purpose

Hyperthermic intraperitoneal chemotherapy (HIPEC) is an addition to the treatment of advanced stage III ovarian cancer consisting of interval cytoreductive surgery (CRS) and neo-adjuvant chemotherapy. The purpose of this study was to perform a cost effectiveness analysis and assess the organizational implications of HIPEC for ovarian carcinoma (OV-HIPEC).

Materials and Methods

A Markov model comparing OV-HIPEC to interval cytoreductive surgery (CRS) was build. A societal perspective from the Netherlands and a time horizon of five years were used. A Monte Carlo simulation with 1000 iterations was carried out. Recent data from a randomized controlled trial (OV-HIPEC1 study) on the effectiveness of both treatments was used. Cost data was derived from treatment protocols, standard prices and cost calculations. Health outcome data was derived from literature.

Results

Total healthcare costs were € 45,829 (95%-CrI¹ 43,199-48,627) for interval CRS compared to € 56,921 (95%-CrI 53,312-61,100) for OV-HIPEC. OV-HIPEC patients gained 1.93 (95%CrI 1.58-2.25) Quality Adjusted Life Years (QALY) and interval CRS patients gained 1.58 (95%-CrI 1.31-1.85) QALYs. The incremental cost effectiveness ratio was € 31,759/QALY. In the cost effectiveness plane 94.5% of iterations were in the north-east quadrant. Given a willingness to pay threshold of € 80,000/QALY, OV-HIPEC has a probability of being cost effective of 83.3%. Interviews with surgeons revealed surgery capacity to be an essential constraint.

Conclusion

Based on our data, OV-HIPEC has the highest probability to be cost effective in stage III ovarian cancer given the current willingness to pay threshold. Although more expensive than interval CRS, OV-HIPEC does result in a larger gain of QALYs.

¹CrI: Credible Interval

1. Introduction

Ovarian cancer is a frequent type of cancer in women, in the Netherlands the incidence is 8.3 per 100,000 and in Europe the incidence is higher at 20.2 per 100,000 (1, 2). The five year survival of women with ovarian cancer in Europe is 37.6% (3). Due to the absence of clear symptoms and ineffectiveness of screening methods most patients are diagnosed with advanced stage (International Federation for Gynecology and Obstetrics (FIGO) stage III or IV) cancers (4, 5).

Current treatment consists of surgery in which tumor load and peritoneal metastases are removed, primary cytoreductive surgery (CRS). In patients with suboptimal primary CRS or patients who require neo-adjuvant chemotherapy before surgery, interval CRS is performed (6). The majority of patients (70%) will have disease persistency or recurrence within 18 months (7, 8). Given this high number of recurrences new approaches are needed to increase survival for these patients.

One of these new approaches is intraperitoneal (IP) chemotherapy, patients received six cycles of chemotherapy in which the chemotherapeutic agents were administered directly to the abdomen using a catheter (9). Compared to intravenous (IV) chemotherapy only, patient survival improved if patients are given IP chemotherapy (9-11). Some studies demonstrated increased toxicity and complication rate in the IP chemotherapy group with up to 58% of patients not completing treatment (9, 10, 12). Toxicity and complications also results in a lower Health Related Quality of Life (HRQoL) in patients receiving IP chemotherapy compared to IV chemotherapy only (9, 13).

A novel way to administer the chemotherapy intraperitoneally is to perfuse the abdominal cavity with chemotherapeutic agents under hyperthermic conditions directly after interval CRS (HIPEC) (14). Patients with colorectal cancer showed improved survival when undergoing HIPEC treatment (14-16). To assess the clinical effectiveness of HIPEC in patients with stage III ovarian cancer (OV-HIPEC), the Netherlands Cancer Institute (NKI) conducted a phase III trial comparing HIPEC to interval CRS in patients with stage III ovarium cancer.

OV-HIPEC addresses some of the problems such as toxicity and catheter complications and the study carried out demonstrated improved survival (17). The question whether this new treatment for patients with stage III ovarian cancer is cost effective remains. Studies into the use of HIPEC in patients with peritoneal carcinomatosis from a colorectal origin revealed that HIPEC could be cost effective, AUD\$21,290/Life Year gained (LY) and €58,086/LY, depending on the willingness-to-pay (WTP) threshold used (18, 19).

For a new technology to be used, and to be reimbursed, more information is needed regarding cost effectiveness and implementation conditions. Therefore, the objective of this study was to perform a health technology assessment (HTA) of OV-HIPEC versus interval CRS in patients with stage III ovarian carcinoma. The primary outcome of the HTA was the cost effectiveness. The organizational consequences of implementing OV-HIPEC were explored.

2. Methods

The purpose of a HTA is to provide insight in, clinical, economic and organizational implications of the implementation and use of healthcare technology (20). These insights can be used to help healthcare decision making processes. This HTA will briefly summarize the clinical findings regarding OV-HIPEC and will shortly address the patient related outcome of health-related quality of life (HRQoL). This HTA will focus more extensively on the economic evaluation of OV-HIPEC and the organizational implications of its implementation.

2.1 Clinical Effectiveness

The data used in the construction of the model was extracted from the OV-HIPEC trial (17). In this multicenter trial, 245 patients with stage III ovarium cancer who received earlier unsuccessful treatment were randomized to undergo interval CRS. The intervention group (n=122) underwent interval CRS with HIPEC (using cisplatin 100mg/m²) and the control group (n=123) received interval CRS only. During the trial patients first received three cycles (three weeks each) of chemotherapy (carboplatin (AUC 3) and taxol 75 mg/m²) followed by the cytoreductive surgery. After surgery, the patients received three additional cycles of chemotherapy, regimen and dose equal to above mentioned.

2.2 Patient Related Outcomes (HRQoL)

To determine the cost effectiveness of a new technology, health state utilities are needed as a measure of the health-related quality of life (HRQoL) in the form of quality adjusted life years (QALY). In this HTA health state utilities found in research published by *Havrilesky et al.* were used to determine the HRQoL during the different health states in the model (*table 2.1*) (21). These health state utilities were based on time trade off tasks performed by female members of the public and by (former) patients of whom nearly all were diagnosed with FIGO stage III-IV disease (21). For patients needing a stoma a disutility, found in a study among colostomy patients, former patients and members of the public, was used (22). All outcome data and effects were discounted at a rate of 1.5% per year in accordance with Dutch guidelines (23).

2.3 Economic Evaluation

A Markov-model was constructed in Microsoft Excel (Microsoft, Redmond, WA). Both the current treatment and intervention were modelled. The model consisted of three health states: disease free survival, disease recurrence and death (*figure 2.2*). This study was carried out from a societal perspective of the Netherlands. Cycle length was one month and the model had a five-year time horizon.

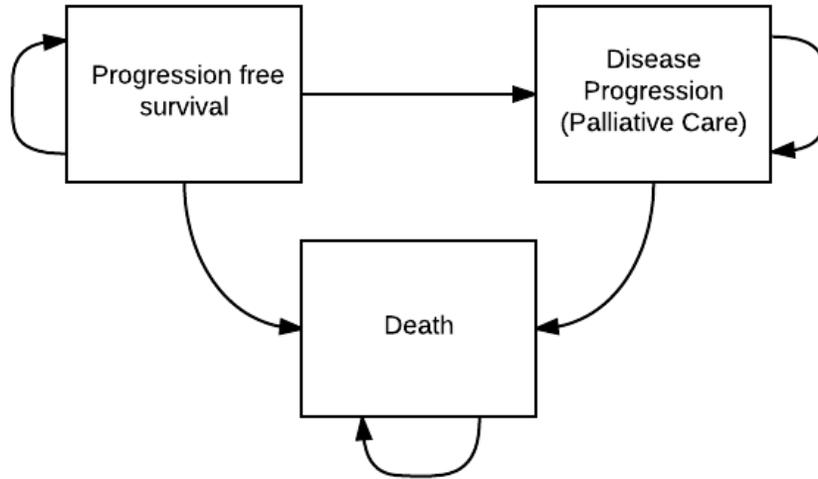


FIGURE 1: MODEL STRUCTURE, THE DIFFERENT HEALTH STATES.

At cycle 0 the patients will enter the model, a total of 1000 women aged 60 will enter the model for each treatment arm. The age of the women corresponds to the mean age of women in the OV-HIPEC trial (17). All patients will receive either the current treatment or the intervention in cycle 0. At the end of each cycle patients will stay or transfer between health states depending on probabilities found in the trial. At the end of cycle 0 post-operative complications and chemotherapy toxicity will be modelled as observed in the trial. Post-operative complications were determined and classed as toxicity grade 1 or 2 and toxicity grade 3 or 4. It is assumed that patients that have a recurrence will be treated according to current treatment guidelines, both for the current treatment as for the intervention patients.

2.3.1 Probabilities and state transfer

Patients transferred between the different health states of the model based on probabilities. These probabilities were based on the Kaplan Meier survival analysis for progression free survival (PFS) and overall survival (OS) found in the OV-HIPEC-1 study (17). For patients treated with interval CRS the PFS probability at 5 years was 4.5% (95%-CI 1.5-13.5) and for HIPEC patients 9.5% (95%-CI 4.9-18.1). Overall Survival probability at 5 years was 25.3% (95%-CI 17.7–36.2) for interval CRS patients and 40.9% (95%-CI 31.7–52.9) for OV-HIPEC patients.

TABLE 1: INPUT PARAMETERS: PROBABILITIES AND HEALTH STATE UTILITIES

	Mean	S.E.	Distribution	Source
<i>Probabilities</i>				
Interval CRS (standard treatment)				
Disease recurrence (per month)	0.0502	0.00502	Beta	(17)
Mortality (per month)	0.0227	0.00227	Beta	(17)
Toxicity Grade 1/2	0.71	0.04	Beta	(17)
Toxicity Grade 3/4	0.24	0.04	Beta	(17)
Stoma	0.11	0.03	Beta	(17)
ICU stay (days)	0.85	0.25	Gamma	(17)
Hospital stay (days)	8.4	0.39	Gamma	(17)
Interval CRS + HIPEC				
Disease recurrence (per month)	0.0385	0.00385	Beta	(17)
Mortality (per month)	0.0148	0.00148	Beta	(17)
Toxicity Grade 1/2	0.7	0.04	Beta	(17)
Toxicity Grade 3/4	0.28	0.04	Beta	(17)
Stoma	0.17	0.03	Beta	(17)
ICU stay (days)	2.05	0.40	Gamma	(17)
Hospital stay (days)	11.00	1.10	Gamma	(17)
<i>Health State Utilities</i>				
Progression free survival	0.83	0.06	Beta	(20)
Newly diagnosed, toxicity grade 1/2	0.60	0.08	Beta	(20)
Newly diagnosed, toxicity grade 3/4	0.49	0.09	Beta	(20)
Recurrent, toxicity grade 1/2	0.40	0.08	Beta	(20)
Recurrent, toxicity grade 3/4	0.47	0.09	Beta	(20)
End stage	0.16	0.06	Beta	(20)
Stoma disutility	0.11	0.05	Beta	(22)

2.3.2 Cost data and analysis

The costs for the treatments and subsequent care were determined using multiple sources and were based on activities performed. The different care processes were identified based on the treatment- and trial protocols. Costs of these different processes were determined according to the *Zorginstituut Nederland* (ZIN) cost manual, the Dutch online database for medication costs and the maximum tariffs set by the Dutch Healthcare Authority (NZa) (23-25). All costs, except medication, costs were calculated in 2014 Euros. Medication costs were expressed in 2017 Euros, these could not be to 2014 Euros since history on medication costs could not be retrieved. Several cost categories could not be calculated using the before mentioned sources. For these categories, internal cost calculations were used. Societal costs were determined based on the ZIN cost manual and data provided by Statistics Netherlands (23, 26). An overview of all costs can be found in *table 2.2*. Total treatment costs, including neo-adjuvant chemotherapy were € 38,051 for interval CRS and €48,638 for HIPEC. Surgery and hospital admission costs only amounted €15,106 for interval CRS and €26,693 for OV-HIPEC. All costs were discounted at a rate of 4% per year (23).

TABLE 2: INPUT PARAMETERS: COSTS

	Unit Cost €	Units	Costs €	S.E.	Subtotal	Distribution	Source
Costs for both treatments							
Chemotherapy (6 cycles)							
Carboplatin (AUC 3) + Paclitaxel (80mg/m ²) ^{a,b}	447.5	18	8,055			Fixed	(22)
Daytreatment	276	18	4,968			Fixed	(21)
Diagnostics							
Laboratory			385			Fixed	(23)
Radiology			948			Fixed	(23)
Pathology			929			Fixed	(23)
Out-patient visits and follow-up							
Consultations	163	13	2,119			Fixed	(21)
Others ^c			198			Fixed	(21)
Societal costs			5,343			Fixed	(21)
		subtotal			22,945		
Interval CRS (standard treatment)							
Surgery			8,000	1,000		Gamma	Internal Calculation
Inpatient stay perioperative							
Ward stay	642	8.40	5,393			Gamma	(21)
ICU stay	2.015	0.85	1,713			Gamma	(21)
		subtotal surgery & admission			15,106		
Interval CRS + HIPEC							
Surgery			14,500	1,500		Gamma	Internal Calculation
Inpatient stay perioperative							
Ward stay	642	11.00	7,062			Gamma	(21)
ICU stay	2.015	2.05	4,131			Gamma	(21)
		subtotal surgery & admission			25,293		
Other Healthcare costs							
Complications							
Toxicity 1/2			50	15		Gamma	Internal Calculation
Toxicity 3/4			750	125		Gamma	Internal Calculation
Stoma			1,500	250		Gamma	Internal Calculation
Recurrence care			11,816	1,000		Gamma	Internal Calculation

^a Assumes mean body surface area of 1.7 m², a weight of 70 kg and a GFR of 75 ml/min

^b Includes materials and pre-medication (Dexamethason (8mg), Clemastine (2mg) and Ranitidine (150mg))

^c Others are consultations by physiotherapists and dieticians.

2.3.3 Primary outcomes and uncertainty analysis

The primary outcome of the model was the incremental cost effectiveness ratio (ICER). The ICER was calculated by dividing the incremental costs by the incremental quality adjusted life years (QALY), see equation 2.1.

$$ICER = \frac{C_i - C_s}{E_i - E_s} = \frac{\Delta C}{\Delta E} \quad (2.1)$$

EQUATION 2.1: ICER CALCULATIONS: C_i = COSTS OF INTERVENTION (€), C_s = COSTS OF STANDARD CARE (€), E_i = EFFECTS OF INTERVENTION (QALY), E_s = EFFECTS OF STANDARD CARE (QALY).

A probabilistic sensitivity analysis (PSA) using a Monte Carlo Simulation, in which the simulation of 1000 patients per treatment arm is repeated a thousand times, was carried out. The corresponding ICERs for each of the iterations were illustrated in a cost effectiveness plane. Cost effectiveness acceptability curves (CEAC) were constructed to demonstrate the probability of cost effectiveness. In CEAC the WTP for a certain health benefit is set against the probability of not breaching the threshold. In the Netherlands the informal threshold for the WTP lies at €80,000 per QALY, this threshold was used to determine the cost effectiveness of OV-HIPEC (27).

2.3.4 Sensitivity analysis

To determine which of the input parameters had the largest impact on the cost effectiveness of OV-HIPEC one-way sensitivity analyses were performed. Analyses were performed that showed the effect of changing the mean of all individual input parameter with plus or minus 20%. Subsequently a tornado diagram was constructed.

The costs of performing the OV-HIPEC procedure were based on a combination of procedural, standardized and internal (NKI-AVL) cost calculations. As this can vary in e.g. other hospitals, with other patients, we addressed this uncertainty by calculating the maximum cost of the procedure in the deterministic model without breaching the WTP thresholds.

3. Results

3.1 Mean results

The mean results demonstrated that OV-HIPEC is more effective compared to interval CRS however, the model also demonstrated that OV-HIPEC is costlier. The total healthcare costs of OV-HIPEC were €56,921 (95%-CrI¹ 53,312-61,100) compared to €45,829 (95%-CrI 43,199-48,627) for interval CRS. Patients treated with OV-HIPEC gained 3.42 (95%-CrI 3.19-3.67) life years versus 2.83 (95%-CrI 2.56-3.12) life years for patients receiving interval CRS only. This resulted in a cost per life year (LY) of €18,821/LY. Taking the quality of life into account, OV-HIPEC patients gained 1.93 (95%CrI 1.58-2.25) QALYs whereas interval CRS patients gained 1.58 (95%-CrI 1.31-1.85) QALYs. This resulted in an incremental cost effectiveness ratio (ICER) of €31,759/QALY within the first five years.

3.2 Probabilistic sensitivity analysis

Figure 2 illustrates the cost effectiveness plane to illustrate the distribution of ICER's found with each of the 1000 iterations. 94.5 percent of the dots are in the North-East quadrant which indicates that the OV-HIPEC treatment is in nearly all cases more expensive but more effective compared to interval CRS only.

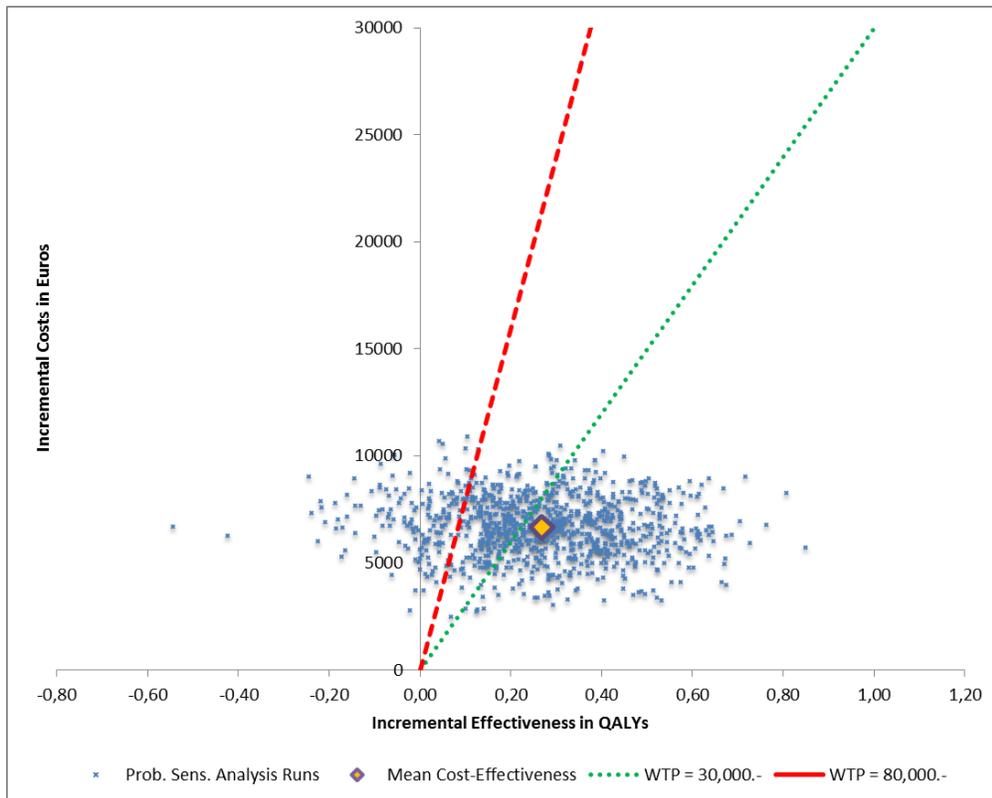


FIGURE 2: THE COST EFFECTIVENESS PLANE SHOWING THE SPREAD OF 1000 ITERATIONS COMPARED TO € 30,000/QALY AND € 80,000/QALY THRESHOLD LINES

¹ 95%-CrI: 95% Credible Interval: Bayesian Statistics are used therefore a credible interval is given not a confidence interval.

To show the probability of OV-HIPEC being cost effective, a cost effectiveness acceptability curve was constructed, *figure 3*. The curve demonstrates that OV-HIPEC does not reach a 100% probability of being cost effective before reaching the €80,000/QALY threshold. At the prevailing threshold of €80,000/QALY the probability for OV-HIPEC being cost effective compared to interval CRS was 83.3%.

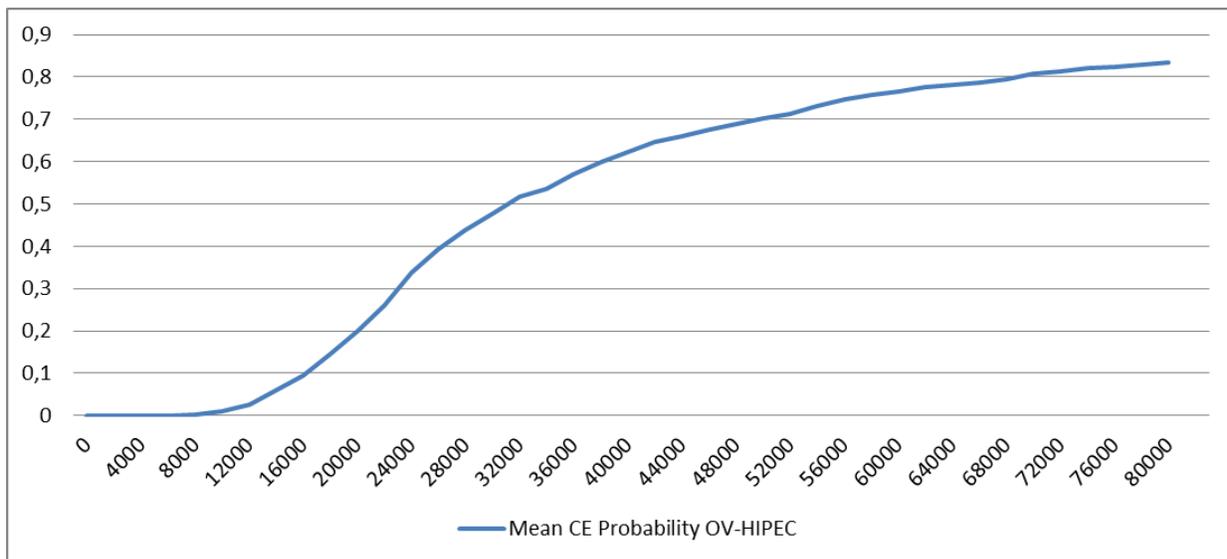


FIGURE 3: BASE CASE ANALYSIS; COST EFFECTIVENESS ACCEPTABILITY CURVE SHOWING THE PROBABILITY OF OV-HIPEC BEING COST EFFECTIVE GIVEN A CERTAIN WILLINGNESS TO PAY THRESHOLD.

3.3 Uncertainty Analysis

Figure 4 shows the tornado diagram which illustrates the effect of changing each of the input parameter with plus or minus 20% on the ICER found in the model. The analyses demonstrated that the mortality probability for interval CRS has the largest effect on the cost effectiveness, ranging from €55,276/QALY with a 20 per cent decrease in probability to €23,679/QALY with a 20 per cent increase. Other parameters that influence the cost effectiveness are the recurrence probability for interval CRS, mortality probability HIPEC, cost of HIPEC surgery and the recurrence probability for HIPEC. Parameters which did not change has no or limited influence on the cost effectiveness result were recurrence costs, chemotherapy costs, stoma costs and toxicity grade 1/2 and grade 3/4 costs, these parameters were not included in the figure.

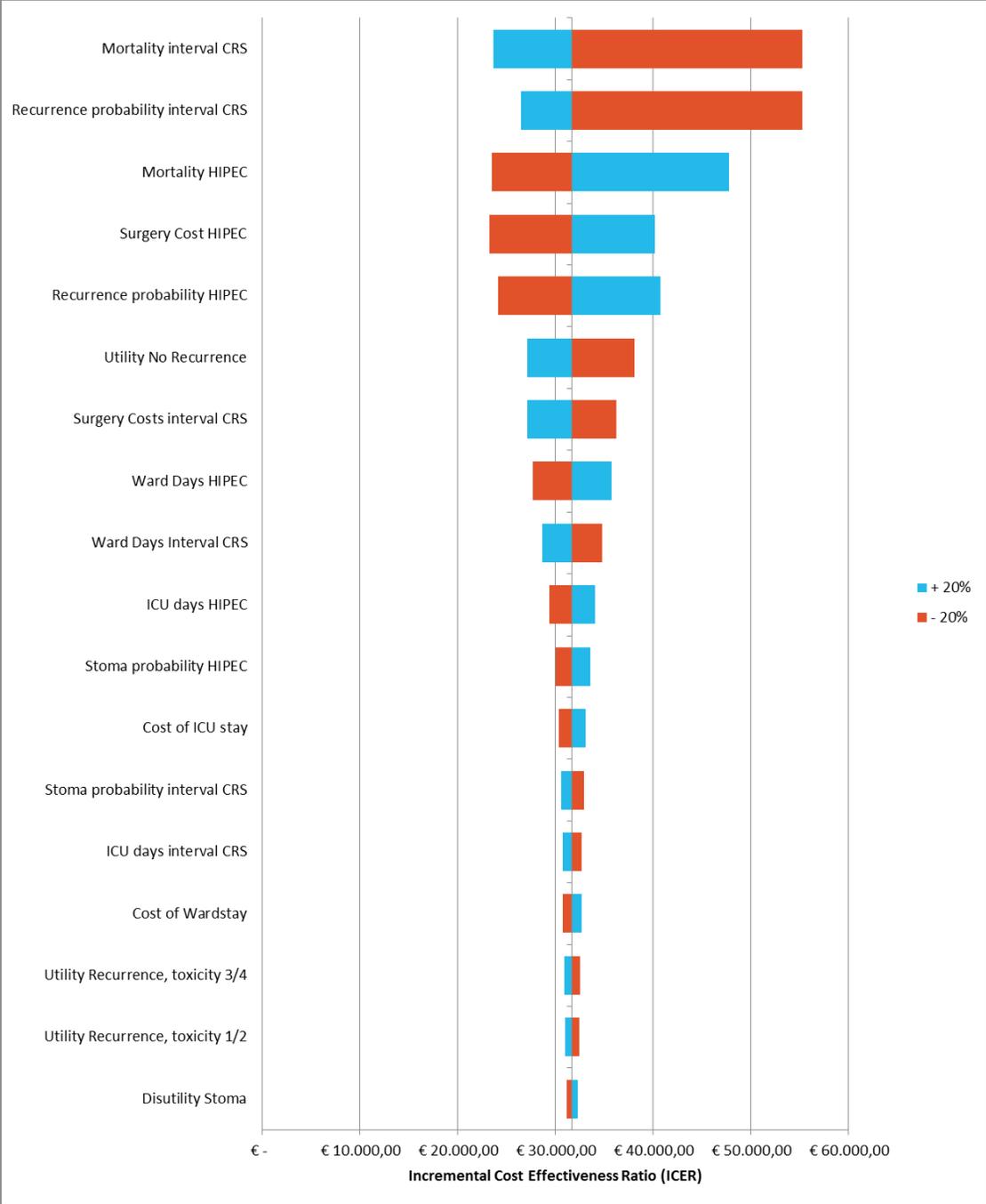


FIGURE 4: TORNADO DIAGRAM SHOWING ONE-WAY SENSITIVITY ANALYSIS RESULTS. LARGER BARS HAVE LARGER EFFECT ON THE COST EFFECTIVENESS.

Alternating the cost for the HIPEC surgery to determine maximum costs whilst still being cost effective resulted in the following maximum costs depending on the WTP threshold. When the WTP threshold is set at €30,000/QALY the maximum charge for the OV-HIPEC surgery is €14,252. Is the WTP threshold set at €80,000/QALY surgery may cost €31,808 for OV-HIPEC to remain cost effective.

4. Discussion and Conclusion

To our knowledge this is the first study to examine the cost effectiveness of HIPEC in patients with ovarian cancer. A limited number of studies investigating the costs and cost effectiveness of HIPEC in colorectal cancer exist. The costs for surgery and admission found in this study were €26,693 for OV-HIPEC. Bonastre *et al.* found a cost of €33,659 per patient for surgery and admission (19). A different study by Chua *et al.* found a total cost of AUD\$66.148 (€44,510, 1 AUD\$ = €0.672, 8/6/2017) for each patient (18). whereas a study in Italy found costs of €36,015 for HIPEC procedures (28). Reasons for these differences could be that the chemotherapeutic agents used for HIPEC in colorectal cancers differ from the agents used in OV-HIPEC. In addition, these studies revealed longer ward and ICU stay. These are also reasons why the ICER found in this study differs from the two earlier cost effectiveness studies by Chua *et al.* and Bonastre *et al.* There were two studies that found similar or lower costs compared to this study, an Italian study found costs of €21,744 (29). Another European study in Greece found costs of €15.67, the main reason for this difference is that ward days and ICU days are considerably less expensive in Greece than in the Netherlands (30).

Surgery time was a substantial driver of treatment costs for OV-HIPEC, as were the number of ICU admissions. The deviation in the costs for surgery and recurrence care were main drivers of the variability in outcomes. The one-way sensitivity analysis demonstrated that the recurrence and mortality probability, together with the costs for HIPEC surgery, were significant in the model. The results of the sensitivity analysis revealed that OV-HIPEC still is cost-effective even if the input parameters vary with up to 20 percent. This was expected since the principal differences in costs and effects are determined by these variables. Other variables such as recurrence costs, chemotherapy costs, stoma costs and costs related to toxicity (both, grade 1/2 and grade 3/4) had little to no effect on the cost effectiveness. This could be explained by the point that these variables were the same for both treatment arms and the probability of experiencing these complications differed little.

This study demonstrated that OV-HIPEC is cost effective in the Netherlands. It is not possible to indicate whether OV-HIPEC will be cost effective in other countries with other healthcare systems. The costs and tariffs used in this analysis are specific to the Netherlands, other countries use different systems of costing and tariffs. New treatments must be included in guidelines before patients can be treated. If OV-HIPEC is included in national guidelines the introduction of OV-HIPEC will have some implications. To determine what the implications can be and which barriers might exist when OV-HIPEC is introduced in the Netherlands, four gynecological surgeons were interviewed, see *appendix A* for interview scheme. The interviews revealed that operating room capacity in the Netherlands will be a crucial barrier for the uptake of OV-HIPEC in the Netherlands

The four surgeons were unanimous in their estimation of the current maximum capacity of the HIPEC and gynecological centers in the Netherlands. They estimated that approximately 280 patients per year can be treated with OV-HIPEC under current conditions. Each year roughly 700 patients with stage III ovarian cancer receive treatment, of whom 460 are eligible for OV-HIPEC treatment. This means that

the centers able to provide OV-HIPEC can treat about 60% of patients, the remaining patients can be treated in centers that offer gynecological oncological surgery only. Applying these numbers to the model results in a ICER of €24,999/QALY, a visual representation of the new model layout can be found in *Appendix B*. The surgeons indicated that choices need to be made regarding increased funding or shifting hospital focus areas to ensure accessibility of care. Some of these choices will likely not be easily implantable. Centralization of care is associated with lower risk of in-hospital deaths, reduced length of stay and lower healthcare costs (31, 32).

When introducing a new treatment, surgeons and other staff members need to familiarize themselves with the new procedures and the execution of new treatments, known as a learning curve. The existence of a learning curve may have an influence on the cost effectiveness since complications may occur more frequent and outcomes could be worse than expected. During the interviews the surgeons indicated that in their experience there was little to no existence of a learning curve. At the time, there were no studies evaluating learning curves in OV-HIPEC. There were, however, several studies addressing learning curve effects in the use of HIPEC in other types of cancer, mainly colorectal cancer. Studies demonstrated that approximately 130-140 patients need to be treated to acquire expertise in the procedure (33, 34). Another study found that 90 patients were needed to improve oncological outcomes and 180 patients for surgical outcomes (35). The surgeons interviewed indicated that since they performed the surgeries together with gastroenterology surgeons they relied on their experiences with HIPEC. Studies have also revealed that tutoring surgeons and institutions who are introducing HIPEC decreases the number of patients needed to be treated before outcomes improve (36, 37). During the OV-HIPEC no data was collected on the frequency of complications of each individual surgeon. Therefore, a more in depth analysis on whether a learning curve is present was not possible. In future research data on learning curves should be acquired.

There are some limitations of this study. The model used in this study is a simplified version of reality. The design of the model relies on trial and treatment protocols. It is possible that in daily practice patient characteristics or preferences make it desirable to deviate from these protocols. During the costs analysis, it became apparent that it was not possible to precisely determine the cost associated with the palliative stage of care. An explanation might be that not all patients participating in the trial completed treatment in the participating centers. This can also mean that treatment for recurrent disease or palliative care has taken place elsewhere, making it difficult to determine the precise costs. Another limitation regarding the costs analysis could be that some of the costs used in the determination of the total costs for the treatment were retrieved from the ZIN-manual. This means that these costs are theoretical and may not reflect true costs as there is a possibility of overestimating costs. The time horizon of this model was five years since there was insufficient data to extend this horizon. Therefore, it is recommended to update the follow-up of the OV-HIPEC-1 study in the future, the additional data can be used to extend the time horizon of this model.

A final limitation is the data on the HRQoL. Even though HRQoL was collected during the trial assessing the effectiveness of OV-HIPEC, it was not possible to use this data in the current model. At the time of this study the data on the HRQoL was not yet complete and ready for analysis. Furthermore, the data was collected using EORTC questionnaires which are not easily translatable to health state utilities.

This study demonstrated that OV-HIPEC is cost effective in the Dutch setting and therefore it could be argued that OV-HIPEC should become available to all eligible patients. The question whether this treatment should be reimbursed in the Netherlands is one to be answered by policymakers. This, and subsequent studies, can only aid in making such decisions as many other factors play a role in this process (27). In the near future, an application for reimbursement under the Dutch “coverage with evidence development program” will be made. The purpose of this application is for OV-HIPEC to be reimbursed in the basic health insurance whilst performing additional trials and cost effectiveness studies.

Additional health technology assessments concerning OV-HIPEC are recommended. These new studies should be performed concurrently with trials evaluating the effectiveness of OV-HIPEC as first line treatment. Executing HTA’s alongside clinical trials will result in more detailed cost data, HRQoL data can be measured with tools that are suitable for HTA’s thus making the methods better reflect international guidelines for cost effectiveness studies alongside clinical trials (38). Another benefit of performing studies alongside clinical trials is the possibility to gather more detailed data on issues concerning capacity and learning curves.

This study demonstrated that although OV-HIPEC is more expensive than interval CRS, patients also gain more QALY’s. Given the WTP threshold of €80,000/QALY, OV-HIPEC is cost effective compared to interval CRS in this group of patients with a probability of 83.3%. As far as the organizational aspects are concerned, the capacity to perform OV-HIPEC interventions is a crucial barrier for the successful implementation of OV-HIPEC. Therefore, choices will have to be made to accommodate all patients eligible for this new treatment.

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Appendix A: Interview setup

Below is the setup used in the semi-structured interviews with the gynecological oncologists, in Dutch.

1) **Ervaring**

- a) *Hoelang al aan het werk als chirurg?*
- b) *Hoeveel OK's bij stage III ovariumcarcinoom?*
- c) *Hoeveel HIPEC's uitgevoerd? (ook andersoortige dan OV-HIPEC)*

2) **Learningcurve**

- a) *Na hoeveel OK's optimale ervaring?*
 - i) *Eigen functioneren*
 - ii) *Zorgketen / logistiek in centrum*
 - iii) *Wat waren hierin steunende factoren?*
- b) *Na hoeveel tijd (weken/maanden/jaren) optimale ervaring?*
- c) *Hoe was de training?*
 - i) *Door wie?*
 - ii) *Op afstand of hands-on?*
 - iii) *Hoe lang nog achtervang?*
 - iv) *Wat was de ervaring met deze training?*

3) **Capaciteit voor OV-HIPEC in centrum en NL**

- a) *Capaciteit in Centrum*
 - i) *Hoeveel OV debulkings kunnen jullie per jaar doen?*
 - ii) *Hebben jullie vaste dag per maand/week waarop dit gebeurt?*
 - iii) *Hoeveel OV-HIPEC zouden jullie per jaar kunnen doen?*
- b) *Capaciteit in NL*
 - i) *Hoeveel OV-HIPEC zouden er per jaar in NL gedaan kunnen worden?*
 - ii) *Kunnen hiermee alle patiënten geholpen worden?*
 - iii) *Wat moet er veranderen om alle patiënten te faciliteren?*
 - iv) *Is het wenselijk dat het aantal centra waar OV-HIPEC uitgevoerd kan worden vergroot wordt?*

4) **Implementatie in de Kliniek**

- a) *Welke stappen heeft u moeten ondernemen om OV-HIPEC ingrepen uit te kunnen voeren?*
- b) *Heeft u de ervaring dat een van deze stappen bijzonder moeilijk te nemen is?*
- c) *Hoe lang heeft de implementatie geduurd?*
- d) *Welk van de genoemde stappen zou in uw ogen een barrière kunnen zijn voor het invoeren van OV-HIPEC?*
- e) *Wat is volgens u de grootste bedreiging voor een brede implementatie van OV-HIPEC in Nederland?*
- f) *Kunt u nog andere mogelijke bedreigingen bedenken?*

5) **Volumeverschillen tussen instellingen**

- a) *Wat denkt u dat een reden kan zijn voor de verschillen in aantal geïncludeerde patiënten per instelling?*
- b) *Welke stappen zouden er gezet moeten worden om deze oorzaken weg te nemen?*
- c) *Denkt u dat deze oorzaken ook eventuele barrières zijn voor brede implementatie van OV-HIPEC?*

Appendix B: Outline of model incorporating capacity constraints

Below is a visual representation of what happens in the model when capacity constraints are considered. Not all patients eligible for treatment with OV-HIPEC can be treated with OV-HIPEC. Some of them will receive interval CRS instead. This has implications for the model and associated outcomes as illustrated below.

