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ORIGINAL RESEARCH ARTICLE

Early Cost-Effectiveness Analysis of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer Patients with Limited Peritoneal Carcinomatosis

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Abstract

Background Gastric cancer patients with peritoneal carcinomatosis (PC) have a poor prognosis, with a median overall survival of 10 months when treated with systemic chemotherapy only. Cohort studies showed that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) might improve the prognosis for gastric cancer patients with limited PC. Besides generating trial data on clinical effectiveness, it is crucial to timely collect information on economic aspects to guide the reimbursement decision-making process. No previous data have been published on the cost(-effectiveness) of CRS/HIPEC in this group of patients. Therefore, we performed an early model-based cost-effectiveness analysis of CRS/HIPEC for gastric cancer patients with limited PC in the Dutch setting.

Methods We constructed a two-state (alive-dead) Markov transition model to evaluate costs and clinical outcomes from a Dutch healthcare perspective. Clinical outcomes, transition probabilities and utilities were derived from literature and verified by clinical experts in the field. Costs were measured using two available representative cohorts (2010–2017): one 'systemic chemotherapy only' cohort and one 'CRS/HIPEC' cohort ($n = 10$ each). Incremental cost-utility ratios (ICURs) were expressed as Euros per quality-adjusted life-year (QALY). We performed probabilistic and deterministic sensitivity, scenario, and value-of-information analyses using a willingness-to-pay (WTP) threshold of €80,000/QALY, which reflects the Dutch norm for severe diseases.

Results In the base-case analysis, CRS/HIPEC yielded more QALYs (increment of 0.68) and more costs (increment of €34,706) compared with systemic chemotherapy only, resulting in an ICUR of €50,990/QALY. The probability that CRS/HIPEC was cost effective compared with systemic chemotherapy alone was 64%. To reduce uncertainty, the expected value of perfect information amounted to €4,021,468. The scenario analyses did not alter the results and showed that treatment costs, lifetime health-related quality of life and overall survival had the largest influence on the model.

Conclusions The presented early cost-effectiveness analysis suggests that adding CRS/HIPEC to systemic chemotherapy for gastric cancer patients with limited PC has a good chance of being cost-effectiveness compared with systemic chemotherapy alone when using a WTP of €80,000/QALY. However, there is substantial uncertainty in view of the current available data on effectiveness. Results from the ongoing phase III PERISCOPE II trial are therefore crucial for further decisions on treatment policy and its cost-effectiveness.

1 Introduction

Worldwide, gastric cancer ranks fifth in cancer incidence and fourth in cancer-related mortality [1]. The incidence of gastric cancer has declined from 1358 to 1042 cases per year in The Netherlands from 2008 to 2017 [2]. However, the prognosis of gastric cancer remains very poor due to a high rate of locally advanced and metastatic disease at the time of diagnosis [3]. Common metastatic sites are the liver (48%), peritoneum (32%), lung (15%), and bone (12%) [4].

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Key Points for Decision Makers

This early model-based economic analysis showed that adding cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) to systemic chemotherapy for gastric cancer patients with limited peritoneal carcinomatosis may be a cost-effective treatment option.

To improve cost-effectiveness, efforts should concentrate on enhancing all aspects of health-related quality of life (HRQoL) related to the procedures. Collecting HRQoL data for all treatment options and identifying factors influencing HRQoL are crucial for better decision making.

Decision makers should be aware of the significant uncertainty in the current analysis due to limited data and its retrospective design. However, the early analysis can help decision makers to make informed resource allocation decisions and research prioritisation, while waiting for the results of the ongoing randomised controlled trial.

In a Dutch cohort, the median survival for patients with synchronous peritoneal metastases was 10 months when treated with systemic chemotherapy [2].

A potential new treatment modality could be hyperthermic intraperitoneal chemotherapy (HIPEC), which allows for high concentrations of cytotoxic drugs in the abdominal cavity with limited systemic exposure [5]. HIPEC in combination with cytoreductive surgery (CRS) has shown improved survival for patients with peritoneal carcinomatosis (PC) from ovarian or colorectal malignancies [6, 7].

CRS/HIPEC is a heavy procedure with a non-negligible risk of postoperative complications and diminished quality of life. There is no high-level evidence showing that this treatment modality provides a survival benefit for patients with PC from gastric cancer [8]. A recent meta-analysis identified 12 randomised controlled trials (RCTs) investigating the role of HIPEC in the treatment of gastric cancer; in 10 of these RCTs, HIPEC was performed in a prophylactic setting, and 11 of these 12 RCTs were conducted in Asian countries [9]. The two RCTs investigating HIPEC as a treatment modality for gastric cancer patients with PC were relatively small ($n = 68$ and $n = 16$, respectively). In these two studies, patients who underwent CRS/HIPEC had a median survival of 11 months (95% confidence interval [CI] 11–11.3 months) compared with those in the control group who had a median survival of 6.5 months (95% CI 4.3–6.5 months) [9]. This difference did not reach statistical significance, possibly due to the small sample sizes. For CRS/HIPEC in the management of gastric cancer, proper patient selection is crucial. Large nationwide Western cohort studies have shown a beneficial role of CRS/HIPEC, but almost exclusively in patients with limited PC, especially in those with a Peritoneal Cancer Index (PCI) below 7 [10–13]. This subset of patients is expected to derive more benefit from the CRS/HIPEC treatment regimen due to a higher likelihood of achieving complete cytoreduction [9, 14].

The currently ongoing randomised controlled phase III trial 'PERISCOPE II' (Treatment of PERItoneal disease in Stomach Cancer with cytOreductive surgery and hyperthermic intraPEritoneal chemotherapy; NCT03348150) is investigating whether the addition of CRS/HIPEC increases overall survival compared with systemic chemotherapy alone for gastric cancer patients with limited PC [15]. The PERISCOPE II trial is conditionally reimbursed as part of a 'coverage with evidence development' trajectory under the supervision of the Dutch Ministry of Health. This is a programme for promising medical interventions, in which CRS/HIPEC treatment is reimbursed for gastric cancer patients with limited PC, under the condition of participation in the randomised trial [15, 16].

A smooth implementation of novel therapies is enabled by performing a Health Technology Assessment (HTA) alongside the trial. HTA systematically assesses the properties, benefits and impact of a (novel) medical treatment or diagnostic procedure. Generally, such assessment is performed in the form of a cost-effectiveness analysis after a positive phase III trial for reimbursement purposes. Often this process is time-consuming and therefore it is recommended to conduct HTA early in the process in order to anticipate on the outcomes ('early HTA') [17–19].

Performing an early economic analysis alongside an ongoing trial can be beneficial for innovative interventions with potentially life-saving clinical outcomes. This analysis alongside a trial informs researchers and decision makers, facilitating a swift and comprehensive reimbursement decision shortly after the final results of the trial become available [17, 20–22]. Anticipating and addressing relevant input parameters, expediting the assessment process, and complementing the trial with existing evidence are key advantages of the early economic model [17, 20–22]. Moreover, its strategic role in potentially securing or withholding from additional funding, especially in the case of protracted accrual, further reinforces its importance. In the current case, the early economic analysis can contribute valuable insights into the evaluation of CRS/HIPEC for gastric cancer patients with limited PC, aiding in anticipating coverage issues and in translating research findings into evidence-based policy and practice.

Although several cost-effectiveness studies on gastric cancer treatment have appeared in recent years, there is no available information in the literature on the cost-effectiveness of CRS/HIPEC in gastric cancer management.

Therefore, the aim of our study was to perform an early cost-effectiveness analysis of CRS/HIPEC in addition to systemic chemotherapy for gastric cancer patients with limited PC compared with systematic chemotherapy alone in the Dutch setting. In this early HTA, prerequisites for cost-effectiveness, relative importance of input parameters for the model, and prioritisation of further research are investigated [18, 23]. Ultimately, this model could be used iteratively when the results of the currently ongoing PERISCOPE II trial become available [15, 19].

2 Methods

2.1 Research Design and Model Description

A Markov model was constructed using Microsoft Excel™ (Microsoft Corporation, Redmond, WA, USA) comparing the cost-effectiveness of CRS/HIPEC in addition to systemic chemotherapy for gastric cancer patients with limited PC compared with systematic chemotherapy alone. The analysis was performed from the Dutch healthcare perspective, with a cycle length of 1 month and a lifetime horizon to accurately capture the events occurring during the life course in both groups. We distinguished two health states (i.e., alive or dead) in the model because of the relatively short life expectancy of this advanced stage of disease and lack of data on time to progression in the literature (see Appendix A in the electronic supplementary material [ESM]). The model is in accordance with the Dutch guidelines for health economic evaluation and international guidelines for decision-analytic modelling [24, 25].

In the current early cost-effectiveness analysis, we estimated the cost utility, meaning that effects are expressed by quality-adjusted life-years (QALYs). Costs are expressed in 2022 Euros. Because of the early stage, data from several sources were combined in the model [2, 11, 26, 27]. In the following sections, we explain the sources separately for cost, survival, and quality-of-life input.

This study was approved by the Institutional Review Board of the Netherlands Cancer Institute (NCI; IRBd21-247) and follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines for economic evaluations (ESM Appendix B) [28].

2.2 Interventions Under Investigation

The interventions under investigation in this study were systemic chemotherapy only (standard treatment) and systemic chemotherapy with the CRS/HIPEC procedure (experimental treatment).

The diagnostic trajectory (including a computed tomography [CT] scan, gastroscopy, and a staging laparoscopy), rehabilitation care (e.g., physiotherapy and ergotherapy), and the follow-up period (including visits and CT scans at the outpatient clinic) were standardised according to the PERISCOPE II trial protocol [15].

2.3 Cost Input: Patient-Level Data

Two retrospective cohorts ($n = 10$ each) from the NCI were used to calculate healthcare costs, based on the same eligibility criteria as the PERISCOPE II study protocol [15]. The 'CRS/HIPEC' cohort was derived from the expansion cohort of the PERISCOPE I study (2014–2017), a non-randomised, dose-finding, phase I–II trial [29], specifically selecting patients ($n = 10$) who underwent experimental treatment at the appropriate dosage. The 'systemic chemotherapy only' cohort in the current study consisted of 10 patients who received systemic chemotherapy at the NCI from 2010 to 2017. Appendix C in the ESM shows an overview of patient characteristics and inclusion criteria.

All cost data, in the time period from gastric cancer diagnosis to last follow-up or death, were retrieved from the electronic medical records. The costs were grouped into three time periods, namely 'Diagnosis' (including outpatient visits, laboratory research, imaging, endoscopic procedures, and day-care unit admissions), 'Treatment period' (including palliative treatment activities, intensive care stay, overnight hospital stays, outpatient visits, laboratory research, imaging, systemic chemotherapeutic agents, and rehabilitation care), and 'Progression' (including palliative treatment activities (i.e., drainage and radiation therapy), overnight hospital stays, outpatient visits, laboratory research, imaging, day-care unit admissions, systemic chemotherapeutic agents, and rehabilitation care) (see Table 1).

In order to ensure accurate cost estimation, we used a patient with complete data registrations as a representative example for diagnostic treatment activities and the CRS/HIPEC procedure since these procedures consistently comprise the same set of activities and are part of the PERISCOPE II protocol. For instance, the CRS/HIPEC procedure includes the cost components of a staging laparotomy, oxaliplatin and docetaxel, the HIPEC procedure, lymph node extirpation, stomach resection, reconstructive surgery, anaesthesia, and enterostomy. Similarly, we standardised rehabilitation care using a regular 'systemic chemotherapy

Table 1 Input parameters in the base-case model

	Mean	No. of units (*N*)	SE	Distribution	Sources
Utilities					
Alive, CRS/HIPEC	0.74		0.23	Beta	Wilke et al. (2014) [26], Abdel-Rahman et al. (2019) [27]
Alive, systemic chemotherapy only	0.74		0.23	Beta	Wilke et al. (2014) [26], Abdel-Rahman et al. (2019) [27]
Death, CRS/HIPEC	0			Fixed	
Death, systemic chemotherapy only	0			Fixed	
Monthly transition probabilities					
Alive to death, CRS/HIPEC	0.0378		0.0220	Beta	Rau et al. (2019) [11]
Alive to death, systemic chemotherapy only	0.0678		0.0130	Beta	Koemans et al. (2021) [2]
Cost of CRS/HIPEC in addition to systemic chemotherapy					
Diagnostics					
Outpatient visits	€1499	$n = 12$[a]	±20%	Gamma	Standardised[b]
Laboratory research	€1000		±20%	Gamma	Standardised
Imaging (including CT scan)	€167	$n = 1$	±20%	Gamma	Standardised
Endoscopic procedures[c]	€2478		±20%	Gamma	Standardised
Day-care unit admissions	€840	$n = 2$	±20%	Gamma	Standardised
Costs during the treatment period					
CRS/HIPEC procedure[d]	€24,501		±20%	Gamma	Standardised
ICU stay	€7500	$n = 3$	€3909	Gamma	CRS/HIPEC cohort
Overnight hospital stays	€25,287	$n = 27$	€4635	Gamma	CRS/HIPEC cohort
Outpatient visits[e]	€97	Periodically[e]	±20%	Gamma	Standardised
Laboratory research	€858		€182	Gamma	CRS/HIPEC cohort
Imaging[e]	€167	Periodically[e]	±20%	Gamma	Standardised
Systemic chemotherapeutic agents[f]	€4741		€2741	Gamma	CRS/HIPEC cohort
Rehabilitation care[g]	€3749		±20%	Gamma	Standardised
Costs during/after progression					
Palliative treatment activities[h]	€1590		€827	Gamma	CRS/HIPEC cohort
Overnight hospital stays	€3746	$n = 4$	€1139	Gamma	CRS/HIPEC cohort
Outpatient visit	€97		±20%	Gamma	Standardised
Laboratory research	€385		€239	Gamma	CRS/HIPEC cohort
Imaging	€167		±20%	Gamma	Standardised
Day-care unit admissions	€840	$n = 2$	€652	Gamma	CRS/HIPEC cohort
Rehabilitation care[g]	€1204		±20%	Gamma	Standardised
Total costs of CRS/HIPEC in addition to systemic chemotherapy: €80,913 (in the model, periodic outpatient visits and imaging are added for the survivors)					
Cost of systemic chemotherapy only					
Diagnostics					
Outpatient visits	€1499	$n = 12$	±20%	Gamma	Standardised
Laboratory research	€1000		±20%	Gamma	Standardised
Imaging (including CT scan)	€167	$n = 1$	±20%	Gamma	Standardised
Endoscopic procedures[c]	€2478		±20%	Gamma	Standardised
Day-care unit admissions	€840	$n = 2$	±20%	Gamma	Standardised
Costs during the treatment period					
Palliative treatment activities[h]	€5337		€1302	Gamma	Systemic chemotherapy-only cohort
Overnight hospital stays	€14,049	$n = 15$	€4216	Gamma	Systemic chemotherapy-only cohort
Outpatient visit[e]	€97	Periodically[e]	±20%	Gamma	Standardised
Laboratory research	€858		€182	Gamma	Systemic chemotherapy-only cohort
Imaging[e]	€167	Periodically[e]	±20%	Gamma	Standardised
Systemic chemotherapeutic agents[f]	€4741		€2108	Gamma	Systemic chemotherapy-only cohort

Table 1 (continued)

	Mean	No. of units (*N*)	SE	Distribution	Sources
Rehabilitation care[g]	€1204		±20%	Gamma	Standardised
Costs during/after progression					
Palliative treatment activities[h]	€2292		€877	Gamma	Systemic chemotherapy-only cohort
Systemic chemotherapeutic agents[f]	€2678		€1298	Gamma	Systemic chemotherapy-only cohort
Overnight hospital stays	€4683	$n = 5$	€1810	Gamma	Systemic chemotherapy-only cohort
Outpatient visit	€97		±20%	Gamma	Standardised
Laboratory research	€547		€154	Gamma	Systemic chemotherapy-only cohort
Imaging	€167		±20%	Gamma	Standardised
Day-care unit admissions	€1680	$n = 4$	€770	Gamma	Systemic chemotherapy-only cohort
Rehabilitation care[g]	€1204		±20%	Gamma	Standardised
Total costs of chemotherapy only: €45,785 (in the model, periodic outpatient visits and imaging are added for the survivors)					

CRS/HIPEC cytoreductive reduction surgery with hyperthermic intraperitoneal chemotherapy, *CT* computed tomography, *ICU* intensive care unit, *PERISCOPE* Treatment of PERItoneal disease in Stomach Cancer with cytoreductive surgery and hyperthermic intra PEritoneal chemotherapy, *SE* standard error

[a]Indicating the average number (*N*) of overnight hospital stays, day-care unit admissions, ICU stays, and CT scans

[b]We standardised some categories (i.e., diagnostics, CRS/HIPEC procedure, outpatient visits, imaging, and rehabilitation care) according to the PERISCOPE II protocol and a patient with complete registration of all treatment activities

[c]Including laparoscopy and a gastroscopy, which was not standard during the time patients in this cohort were treated, therefore the endoscopic procedures were added for every patient to estimate realistic costs

[d]Including costs of a staging laparotomy, oxaliplatin and docetaxel, the HIPEC procedure, lymph node extirpation, stomach resection, reconstructive surgery, anaesthesia, and enterostomy

[e]Consults and imaging were standardised in the PERISCOPE II protocol; all patients received a consult and CT scan every 3 months for the first 1.5 years and every 6 months thereafter until 3 years after randomisation

[f]A summary of all costs of chemotherapeutic agents used either during the treatment period or during/after progression, i.e., 5-fluorouracil, capecitabine, etc., excluding drug costs of the HIPEC procedure. An overview can be found in Appendix B in the electronic supplementary material

[g]We standardised rehabilitation care using a regular 'systemic chemotherapy only' and 'CRS/HIPEC' patient receiving a combination of physiotherapy, ergotherapy, and advice from a dietician, social worker, and psychologist

[h]Palliative treatment activities include radiation therapy and drainage, to distress symptoms caused by cancer

only' and 'CRS/HIPEC' patient receiving a combination of physiotherapy, ergotherapy, and advice from a dietician, social worker, or psychologist. Furthermore, consults and imaging are standardised in the PERISCOPE II protocol, meaning that all patients receive a consult and CT scan every 3 months for the first 1.5 years and every 6 months thereafter until 3 years after randomisation in the currently ongoing trial. Other cost activities, such as intensive care unit (ICU) stay and laboratory research, were based on the real-world data in the cohorts ($n = 10$ each). In the model, costs for 'Diagnosis' were attributed in cycle 0, and costs for 'Treatment period' were attributed in cycle 0, except for consults and imaging, which were tailored to the according time periods. The costs for 'Progression' were attributed in the cycle where patients go from the alive state to the dead state.

All chemotherapeutic agents administered in either the 'systemic chemotherapy only' or 'CRS/HIPEC' cohorts were used to estimate the cost of chemotherapeutic drugs (see Appendix D). The drug costs of the HIPEC procedure were included in the CRS/HIPEC procedure costs. When dosages were not reported, we assumed a standard dosage for an average body weight of 1.9 m^2 for men and 1.6 m^2 for women [30–32].

Unit costs were based on the maximum tariffs set by the Dutch Healthcare Authority for 2022 [33]. Chemotherapeutic agents and supportive drugs were valued using the Dutch database on drug pricing for the year 2022 [34].

2.4 Survival Input: Estimation of Transition Probabilities

All clinical inputs for the base-case analysis were derived from the literature by back and forward reference searching in PubMed using the keywords 'overall survival OR progression-free survival OR health-related quality of life OR HRQoL OR quality-adjusted life-years OR QALY', 'gastric cancer', and 'peritoneum OR peritoneal', in combination with 'HIPEC' or 'chemotherapy'. The obtained literature was validated by conducting five structured interviews with clinical experts, including five senior oncological surgeons and three surgical residents, to ensure the accuracy and relevance of the selected studies and to potentially identify additional sources. Interviews were held until saturation was reached.

For the systemic chemotherapy group, the article by Koemans et al. (2021) was considered the most relevant (a recent nationwide Dutch study, synchronous peritoneal metastases only, patients treated with systemic chemotherapy) [2]. In that paper, a median overall survival of 10 months was reported. Other studies that were carefully considered, for instance, included those by Chia et al. (2016) and Thomassen et al. (2013), which also found an overall survival of 8–12 months [35, 36]. However, estimates from studies such as these were deemed less relevant due to factors such as the publication date, an incompatible target population, or the study was conducted in an Asian country.

In the case of the CRS/HIPEC group, we chose to include the study by Rau et al. (2020). This selection was based on the study's focus on gastric cancer patients with limited PC in Germany, specifically those with a Peritoneal Index Score ranging from 0 to 6, who underwent CRS/HIPEC [11]. The limited PC score within this study closely aligns with our current study's target population. Median overall survival in this study was 18 months. Unfortunately, available RCTs investigating CRS/HIPEC in gastric cancer were primarily conducted in Asian regions and do not reflect the Dutch population very well [9]. The solitary Western study by Rudloff et al. (2014) was considered less applicable due to its limited sample size ($n = 17$) and high baseline peritoneal cancer scores [37]. Hence, in this instance, the use of two observational studies closely related to our target population in both treatment arms was deemed the most suitable approach to derive estimates for the transition probabilities.

To use the survival data in the Markov model, overall survival per cycle (t) was calculated into transition probabilities (p) using 1-month hazard rates (r), with the following equations: $r = -\text{Inverse}(1 - 0.5)/\text{median\_treatment})$ and $p = 1 - \exp(-\text{rt})$ [38]. Hence, based on an exponential distribution and a median survival time of 10 or 18 months within the cohorts, the 1-month probability of the event of death occurring is approximately 6.78% and 3.78%, respectively. The calculated probabilities can be found in Table 1. General age- and sex-specific mortality rates were not included in this model because they were already accounted for in the survival estimates derived from the literature.

2.5 Utility Input: Health-Related Quality of Life

The utilities were obtained from the literature and validated by the clinical experts, as described above. A baseline health-related quality of life (HRQoL) of 0.74 was used, as reported in the studies by Wilke et al. (2014) and Abdel-Rahman et al. (2019), who investigated similar study populations [26, 27, 39]. To our knowledge, there are no publications available wherein the effects of CRS/HIPEC on HRQoL with the EQ-5D in gastric cancer patients have been reported. In ovarian cancer and colorectal cancer patients, it was found that HRQoL decreased during the first 3–12 months after a CRS/HIPEC procedure [40–43]. In patients undergoing systemic chemotherapy, it is generally reported that there is no change in regard to HRQoL level until progression [43]; however, during treatment days, HRQoL might be impacted. Therefore, our baseline assumption was that HRQoL remained equal between both groups (0.74), and several scenarios devaluing HRQoL for a certain period of time were modelled using utility decrements (see Table 1, the Deterministic Sensitivity Analyses and scenarios section).

2.6 Data Analysis

Costs were discounted at 4% annually and effects at 1.5%, as recommended by the Dutch costing manual [24]. A hypothetical cohort of 1000 patients was used to simulate the incremental cost-utility ratio (ICUR), which was calculated as follows:

$$\text{ICUR} = \frac{(\text{Cost of CRS/HIPEC with systemic chemotherapy} - \text{Cost of systemic chemotherapy alone})}{(\text{QALYs of CRS/HIPEC with systemic chemotherapy} - \text{QALYs of systemic chemotherapy alone})}$$

2.7 Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was performed by plotting ICURs on an incremental cost-effectiveness plane using 10,000 Monte Carlo simulations of 1000 patients. Gamma distributions were used to estimate the uncertainty surrounding the costs, and beta distributions were used for utilities and transition probabilities. Cost-effectiveness acceptability curves (CEACs) were constructed to demonstrate the probability of the incremental net monetary benefit (NMB) of CRS/HIPEC being positive for different values of willingness-to-pay (WTP) thresholds. The NMB is calculated for each iteration and both treatments using the formula:

$$\text{NMB} = (\text{Total QALYs} * \text{WTP threshold} - \text{total cost})$$

In The Netherlands, the informal threshold for a WTP of €80,000 per QALY is justified due to the severity of metastatic gastric cancer [44, 45].

2.8 Deterministic Sensitivity Analyses and Scenarios

The sources and assumptions were tested for validity through verification interviews with the clinical experts. The scenarios regarding the potential future implementation of the procedure were drafted as a result of these interviews.

A series of one-way and structural deterministic sensitivity analyses was performed to investigate the robustness of the model. In particular, the following input parameters were increased and decreased with 20% for the CRS/HIPEC group: lifetime HRQoL, HRQoL in the first 9 months, median overall survival, and total costs. Moreover, we analysed the impact on the ICUR when discounting was altered for either costs or QALYs for both groups. Ideally, this sensitivity analysis is guided by estimates of uncertainty in the underlying parameters [28]. However, in the absence of precise uncertainty estimates, the use of a ± 20% range for sensitivity analysis offers a pragmatic means to estimate the potential impact of parameter variations, and provides a baseline understanding of relative parameter importance.

Additionally, two scenarios were modelled (Table 2)—one regarding the HRQoL, including a reduction in HRQoL in the first 9 months in the CRS/HIPEC group (scenario 1A), a devaluation of HRQoL of, in total, 1 month for the systemic chemotherapy-only group (scenario 1B), and a combination of the former two scenarios (scenario 1C); and one scenario wherein survival estimates were based on the patient-level data used for the cost input; the 'systemic chemotherapy only' ($n = 10$) and 'CRS/HIPEC' cohorts ($n = 10$) [scenario 2] (Appendix E).

2.9 Value-of-Information Analysis

We performed a value-of-information (VOI) analysis based on the current available data (data used in the model) to estimate the total value of further research to reduce decision uncertainty (of making the wrong choice), leading to minimal opportunity losses. Therefore, the expected value of perfect information (EVPI) was calculated. In the EVPI analysis, we assumed that there was no uncertainty in any of the parameters used in the model. In other words, the EVPI is equal to the expected net benefit using perfect information, minus the expected net benefit using the currently available imperfect information, by averaging the NMB over the joint distributions of all parameters in the model for 10,000 iterations [46]. For this analysis, we estimated that per year, 30 gastric patients would be eligible for CRS/HIPEC in The Netherlands, as is indicated by the estimated number of inclusions for the currently ongoing PERISCOPE II trial. In case the CRS/HIPEC is performed for the coming 15 years, and applying a discount of 4% [47, 48], the effective population would amount to 347 patients. The CHEERS-VOI reporting standards have been followed where applicable [49].

3 Results

Base-Case In the base-case analysis, the mean total costs for CRS/HIPEC plus systemic chemotherapy were €77,039, and €42,333 for systemic chemotherapy alone (Table 2), resulting in an incremental cost of + €34,706 per patient for the CRS/HIPEC group. The mean total amount of lifetime QALYs was 1.53 and 0.85, respectively, per patient in favour of the CRS/HIPEC group. Subsequently, an average amount of incremental QALYs of + 0.68 was noted. This indicates an ICUR of €50,990/QALY per patient.

Probabilistic Sensitivity Analysis Most of the 10,000 iterations of the 1000 samples in the incremental cost-effectiveness plane were in the North-East quadrant (84.3%), meaning that CRS/HIPEC is likely to be more expensive but may generate more QALYs (see the scatter plot shown in Fig. 1). Furthermore, the point estimate (i.e., mean result) on the scatter plot indicated that the CRS/HIPEC group is likely below the €80,000/QALY threshold. Specifically, the mean incremental costs of the 10,000 iterations were €34,865 (97.5% credibility interval [CrI] €168–€72,762) and lifetime incremental QALYs were 1.20 (97.5% CrI − 0.42 to 4.80).

The CEACs, representing the probability of either CRS/HIPEC or systemic chemotherapy alone having a positive NMB for a range of WTP thresholds, indicated that for a WTP threshold of €45,000 and €80,000, the probability was

Table 2 Deterministic incremental cost-utility results for the base case and four scenarios

	Costs	QALYs	Incremental costs	Incremental QALYs	ICUR
Base-case results					
CRS/HIPEC	Total cost: €77,039 Diagnosis and treatment costs (cycle 0): €72,884	1.53	€34,706	0.68	€50,990
Systemic chemotherapy only	Total cost: €42,333 Diagnosis and treatment cost (cycle 0): €32,436	0.85			
Scenario 1A: Decrement of HRQoL in the first 9 months to 0.50 and 0.60 for the CRS/HIPEC procedure due to surgery					
CRS/HIPEC	€77,039	1.39; 1.45	€34,706	0.55; 0.60	€63,614; €57,665
Systemic chemotherapy only	€42,333	0.85			
Scenario 1B: Decrement of HRQoL during treatment days (1-month total) to 0.50 and 0.60 for the systemic chemotherapy-only group					
CRS/HIPEC	€77,039	1.53	€34,706	0.70; 0.69	€49,629; €50,187
Systemic chemotherapy only	€42,333	0.83; 0.84			
Scenario 1C: Combination of scenarios 1A and 1C					
CRS/HIPEC	€77,039	1.39; 1.45	€34,706	0.56; 0.61	€61,510; €56,641
Systemic chemotherapy only	€42,333	0.83; 0.84			
Scenario 2: Overall survival increased to 26.9 months (instead of 18 months) and 13.4 months (instead of 10 months) for the CRS/HIPEC and systemic chemotherapy-only groups, respectively, based on our patient-level data (n = 20)					
CRS/HIPEC	€76,276	2.25	€33,953	1.11	€30,588
Systemic chemotherapy only	€42,333	1.14			

CRS/HIPEC cytoreductive reduction surgery with hyperthermic intraperitoneal chemotherapy, *HRQoL* health-related quality of life, *ICUR* incremental cost-utility ratio, *QALYs* quality-adjusted life-years

50.0% and 64.0% that CRS/HIPEC is cost effective, respectively (Fig. 2).

Deterministic Sensitivity, Scenario, and Value-of-Information Analyses The deterministic sensitivity analysis showed the impact of increasing or decreasing key parameter estimates on the ICUR. A 20% improvement in median overall survival (from 18 to 22 months), lifetime HRQoL (from 0.74 to 0.88), or total costs (from €80,913 to €64,730) in the CRS/HIPEC group resulted in more favourable cost-effectiveness ratios, with ICURs below the acceptable WTP of €80,000/QALY (€33,810, €36,087 and €27,214, respectively). On the other hand, a 20% decrease in median overall survival (from 18 to 14 months) or lifetime HRQoL (from 0.74 to 0.59) resulted in ICURs of €103,209 and €96,886, respectively, exceeding the acceptable WTP. Other 20% devaluations of key parameters did not result in ICURs above the acceptable €80,000/QALY. Results are presented in the tornado diagram shown in Fig. 3.

The study's scenario analyses revealed the potential impact of different HRQoLs (scenarios 1A, 1B and 1C) and survival estimates based on patient-level data (scenario 2) on the ICURs. Scenarios 1A, 1B and 1C had incremental QALYs of 0.55 (scenario 1A) to 0.70 (scenario 1B) per patient compared with the base-case incremental QALYs of 0.68. Scenario 2 had an increase in incremental QALYs per patient to 1.11. Moreover, scenario 2 resulted in slightly lower incremental costs of €33,943 compared with €34,706 in the base case. This resulted in ICURs below the acceptable WTP for each scenario, i.e., €63,614 to €57,665 for scenario 1A, €49,629 to €50,187 for scenario 1B, €61,510 to €56,641 for scenario 1C, and €30,588 for scenario 2. The data are presented in Table 2.

In the EVPI analysis, based on a patient population of the coming 15 years (n = 347) in The Netherlands, the cost to reduce all uncertainty amounted to €4,021,468. When leaving out the discount on the expected effective population for the coming 15 years, the EVPI amounted to €5,208,963.

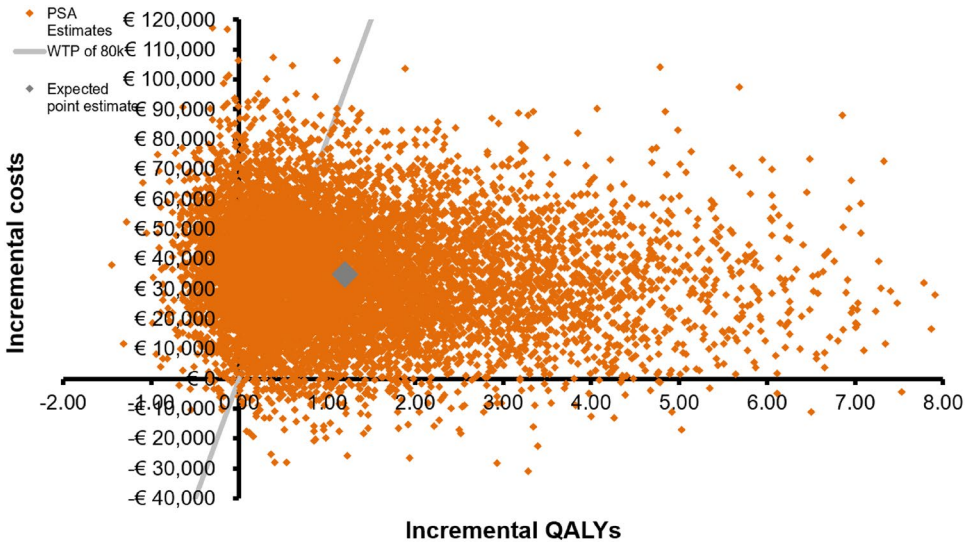

Fig. 1 Base-case incremental cost-effectiveness plane of CRS/HIPEC versus systemic chemotherapy only for gastric cancer patients with limited peritoneal carcinomatosis. Costs are expressed in Euros and effects are expressed in QALYs. Each orange dot represents one of the 10,000 iterations within the PSA. The WTP threshold and point estimate (i.e., mean result) are depicted as a grey line and a diamond, respectively. *CRS/HIPEC* cytoreduction surgery with hyperthermic intraperitoneal chemotherapy, *PSA* probabilistic sensitivity analyses, *QALYs* quality-adjusted life-years, *WTP* willingness-to-pay

4 Discussion

In this early cost-effectiveness analysis of CRS/HIPEC in addition to systemic chemotherapy compared with systemic chemotherapy alone in gastric cancer patients with limited PC, we found that CRS/HIPEC can generate more QALYs on average per patient (1.53) than systemic chemotherapy alone (0.85). Additionally, it showed that this novel treatment would increase costs per patient (€77,039) compared with systemic chemotherapy alone (€42,333). This resulted in an ICUR of €50,990/QALY, which is below the WTP of €80,000/QALY, an accepted threshold to use in The Netherlands for severe diseases. Therefore, the addition of CRS/HIPEC to systemic chemotherapy can be considered a potentially cost-effective treatment option for gastric cancer patients with limited PC according to the current data, due to the increase in QALYs per patient compared with systemic chemotherapy alone. However, there was significant uncertainty surrounding the input parameters in the model, as is common in early analyses, which reflects the modest probability of a positive NMB (69%) [Fig. 2], and a relatively large spread of the 10,000 iterations in the probabilistic analysis (Fig. 1).

In the scenario analyses, the ICURs remained within acceptable terms if CRS/HIPEC would decrease HRQoL to an average of 0.5 or 0.6 for the first 9 months after surgery (€63,614–€57,665). However, the ICUR is highly dependent of the duration of decreased HRQoL. In the situation of an impacted HRQoL from diagnosis until death in the CRS/HIPEC group, the ICUR became €96,886 (Fig. 3). This variety emphasises the importance of improving all HRQoL aspects related to this procedure, to collect data on HRQoL in both treatment options, and to identify factors that influence HRQoL [50]. In the current ongoing randomised PERISCOPE II trial, HRQoL questionnaires are obtained from patients in both arms at 3, 9, 15, 24 and 36 months after randomisation [15].

The estimation of costs for the CRS/HIPEC and systemic chemotherapy-only groups in the current study were based on the expansion cohort of the PERISCOPE I study ($n = 10$) and a retrospective cohort from the NCI ($n = 10$). Although these two cohorts are very small, they represent the current clinical trial. Regarding systemic chemotherapy, the type and duration of the chemotherapeutic regimens were fairly heterogeneous, reflecting earlier clinical practice. Due to the small sample sizes in the present analyses and the potential new developments in the coming years, it is likely that the costs as presented in this study will differ from future economic analyses. Following our deterministic sensitivity analysis, this can impact the exact ICUR but is unlikely to finish above €80,000/QALY. When more data are available, it might be interesting to gain insights into the cost-effectiveness of more specific available treatment schemes, especially with the recent adjustment of the guideline to include the addition of immunotherapy to chemotherapy as part of the standard of care in first-line treatment for patients with metastatic gastric cancer with a combined positive score of 5 or higher [51].

To further reduce uncertainty, the EVPI amounted to €4,021,468 in the base-case analysis. The ongoing European multicentre phase III PERISCOPE II trial will provide information on all relevant input parameters (i.e., overall survival, HRQoL, and costs) [15, 48].

The current analyses have some limitations, as is inevitable in this early stage. In particular, the current study had to make assumptions based on existing literature and expert input. For example, the transition probabilities for the systemic chemotherapy-only group was based on a cohort without specific clarification of the PCI score because staging

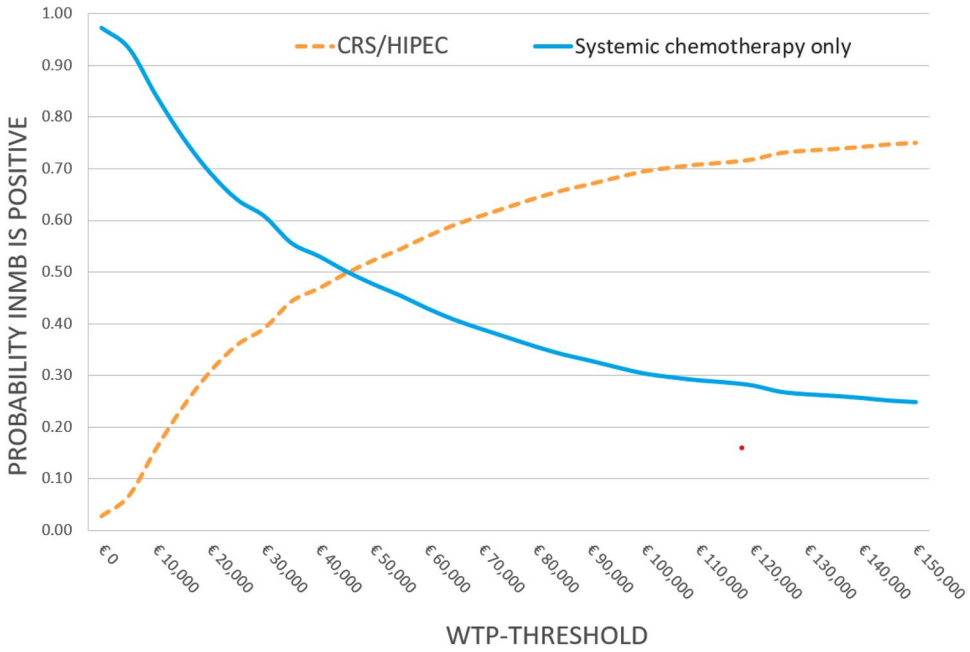

Fig. 2 Base-case cost-effectiveness acceptability curves representing the probability that either CRS/HIPEC or systemic chemotherapy only have a positive INMB for a range of WTP thresholds. When using a WTP threshold of €45,000 or €80,000, the probability is 50.0% and 64.0% that CRS/HIPC is cost effective (orange dotted line), respectively. *CRS/HIPEC* cytoreduction surgery with hyperthermic intraperitoneal chemotherapy, *INMB* incremental net monetary benefit, *WTP* willingness-to-pay

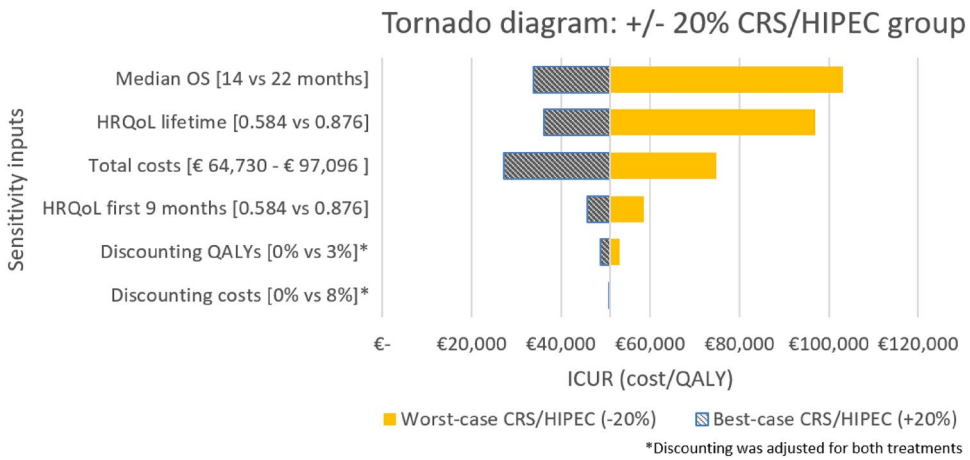

Fig. 3 Tornado diagram showing six univariate sensitivity analyses applied to the CRS/HIPEC group, and demonstrating that the deterministic ICUR is mostly affected when either the median OS or lifetime HRQoL are devalued (in this analysis, by 20%). This may lead to ICURs above the willingness-to-pay threshold of €80,000 per QALY. *CRS/HIPEC* cytoreduction surgery with hyperthermic intraperitoneal chemotherapy, *ICUR* incremental cost-utility ratio, *OS* overall survival, *HRQoL* health-related quality of life, *QALY* quality-adjusted life-year

laparoscopy was not a standard procedure in The Netherlands until it was added to the Dutch national guidelines in 2016. Moreover, the estimation of costs in this study relied on the use of relatively small cohorts. To tackle these limitations, we conducted both scenario analyses and sensitivity analyses, which indicate that the overall conclusions are unlikely to be affected. Moreover, the transition probabilities of both the systemic chemotherapy cohort and the CRS/HIPEC cohort were based on observational studies. These choices were made to relate more to the Dutch context and the inclusion criteria of the PERISCOPE II study. RCT data will be more robust, but with these data, the results are a better fit for our target population. The potential effect of other input transition probabilities was tested in scenario 2, where we were able to make the same conclusion. Last, the efficacy data were based on an unadjusted comparison of separate cohorts and we assumed an exponential distribution of survival. This may introduce biases and confounding factors, potentially impacting the accuracy and reliability of the estimates. After the results of the PERISCOPE II trial are

available, better informed extrapolation methods should be used to estimate the full lifetime horizon [52]. In summary, this model-based study was conducted early on in the process but is a valuable addition to future trial-based economic evaluations despite a relatively large parameter uncertainty, and has the potential to inform research prioritisation.

5 Conclusions

The presented early cost-effectiveness analysis suggests that adding CRS/HIPEC to systemic chemotherapy for gastric cancer patients with limited PC, compared with systemic chemotherapy alone, is potentially cost effective. The ICUR resulted in an ICUR of €50,990/QALY, which is well below the Dutch WTP threshold of €80,000/QALY. This early cost-effectiveness analysis was performed using the current (limited) available data on effectiveness, therefore results from the ongoing phase III PERISCOPE II trial are crucial for further decisions on treatment policy and its cost-effectiveness.

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Declarations

Ethics Approval This study was approved by the Institutional Review Board of the NCI (IRBd21-247).

Availability of Data and Materials The datasets and Markov model used and analysed during the current study are available from the corresponding author on reasonable request.

Code Availability The cost-effectiveness model was developed in Microsoft Excel 365 (Microsoft Corporation). Any additional information about model programming is available from the corresponding author upon request.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflicts of Interest/Competing Interests Valesca P. Retèl and Wim H. van Harten received unrestricted research grants from Agendia BV and Intuitive BV, outside the scope of the current research. Joost G.E. Verbeek, Karen van der Sluis, Marieke A. Vollebergh and Johanna W. van Sandick declare that they have no conflicts of interest in relation to this work.

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Authors' Contributions JV, VR, WvH, and JvS have made substantial contributions to the design and concept of this study. JV, KvdS, and VR collected and analysed data from literature and the 'systemic chemotherapy only' and 'CRS/HIPEC' cohorts. JV and VR constructed the Markov model, and JV wrote the first draft of this manuscript. All authors revised and contributed to subsequent versions of the manuscript, and the final version was approved by all authors.

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