Ann Surg Oncol (2019) 26:1110–1117
https://doi.org/10.1245/s10434-018-07111-y

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Cost-Effectiveness Analysis of Cytoreductive Surgery and HIPEC Compared With Systemic Chemotherapy in Isolated Peritoneal Carcinomatosis From Metastatic Colorectal Cancer

Trevor D. Hamilton, MD, MSc[1,2], Andrea J. MacNeill, MD, MSc[2], Howard Lim, MD, PhD[3], and M. G. Myriam Hunink, MD, PhD[1,4]

[1]Harvard T. H. Chan School of Public Health, Boston; [2]Department of Surgery, University of British Columbia, Vancouver, Canada; [3]Division of Medical Oncology, BC Cancer, Vancouver, Canada; [4]Erasmus Medical Center, Rotterdam, Netherlands

ABSTRACT

Background. Cost-effectiveness evaluations of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis (PC) from metastatic colorectal cancer (mCRC) in the United States are lacking.

Methods. The authors developed a Markov model to evaluate the cost-effectiveness of CRS/HIPEC compared with systemic chemotherapy for isolated PC from mCRC from a societal perspective in the United States. The systemic treatment regimens consisted of FOLFOX, FOLFIRI, bevacizumab, cetuximab, and pantitumumab. The model inputs including costs, probabilities, survival, progression, and utilities were taken from the literature. The cycle length for the model was 2 weeks, and the time horizon was 7 years. A discount rate of 3% was applied. The model was tested for internal and external validation, and robustness was established with univariate sensitivity and probabilistic sensitivity analyses (PSA). The primary outcomes were total costs, quality-adjusted life-years (QALYs), life-years (LYs), and incremental cost-effectiveness ratio (ICER). A willingness-to-pay (WTP) threshold of $100,000 per QALY was assumed.

Results. The ICER for treatment with CRS/HIPEC compared with systemic chemotherapy was $91,034 per QALY gained ($74,098 per LY gained). The univariate sensitivity analysis showed that the total costs for treatment with CRS/HIPEC had the largest effect on the calculated ICER. The CRS/HIPEC treatment was a cost-effective strategy during the majority of simulations in the PSA. The average ICER for 100,000 simulations in the PSA was $70,807 per QALY gained. The likelihood of CRS/HIPEC being a cost-effective strategy at the WTP threshold was 87%.

Conclusions. The CRS/HIPEC procedure is a cost-effective treatment for isolated PC from mCRC in the United States.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-07111-y) contains supplementary material, which is available to authorized users.

First Received: 29 August 2018;
Published Online: 28 January 2019

T. D. Hamilton, MD, MSc
e-mail: trevor.hamilton@vch.ca

More than 135,000 new cases of colorectal cancer are diagnosed in the United States each year.[1] Isolated metastatic disease with peritoneal carcinomatosis (PC) occurs in 13% of cases.[2] Best supportive care portends a poor prognosis, with a median survival period of only 5–7 months.[2]

Improvements in systemic chemotherapy during the past two decades have increased the median survival period to 12–20 months.[3–5] Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for selected patients with PC from metastatic colorectal cancer (mCRC) has demonstrated improved survival.[6–10]

Despite the increasing use of CRS/HIPEC in the United States,[11] the treatment has not been universally adopted.[12] Limited funding or insurance coverage, paucity of randomized clinical trials, and variations in techniques may limit its implementation as a standard treatment option.[13] Few cost-effectiveness analyses (CEAs) have been performed to date,[14,15] and the available CEAs did not incorporate health-related quality of life (HR-QOL) for evaluation. Further health economic evaluations in the United States are required to help guide funding and health policy decisions.[16]

This study aimed to perform a CEA of CRS/HIPEC compared with systemic chemotherapy for isolated PC from mCRC from a societal perspective in the United States.

METHODS

Model

A Markov model was developed to evaluate the cost-effectiveness of CRS/HIPEC compared with systemic chemotherapy for isolated PC from mCRC. Patients treated with CRS/HIPEC were initiated to systemic chemotherapy in the setting of recurrence (Fig. 1). Patients treated with systemic chemotherapy alone were initiated to regimens based on either FOLFOX (folinic acid, fluorouracil, oxaliplatin) or FOLFIRI (folinic acid, fluorouracil, irinotecan) with bevacizumab. Subsequent progression with systemic chemotherapy prompted a regimen switch to second-line treatment with FOLIRI (if FOLFOX was the first-line treatment) or FOLFOX (if FOLFIRI was the first-line treatment). Further progression with systemic chemotherapy prompted a regimen change to third-line treatments, including cetuximab or panitumumab in the setting of K-RAS wild-type tumors. At any point in the treatment, if a decline in functional status or intolerance for chemotherapy precluded systemic therapy options, patients were transitioned to best supportive care. TreeAge Pro Software, Inc. (version 2.1, 2017; Williamstown, MA, USA) was used for the analysis.

Costs were estimated in 2017 U.S. dollars. Utilities ranged from 0 to 1 for each health state. The chosen cycle length for the model was 2 weeks because that is the length of a typical cycle of systemic chemotherapy and the length of a typical hospital stay for CRS/HIPEC. A time horizon of 7 years was chosen because this reflects the long-term survival time for this patient population. A discount rate of 3% was applied to both costs and quality-adjusted life-years (QALYs). Model outputs included total costs, life-years (LYs), QALYs, and incremental cost-effectiveness ratios (ICERs). A half-cycle correction was applied to the model. A willingness-to-pay (WTP) threshold of $100,000 per QALY was adopted for assessment of cost-effectiveness.

Assumptions and Estimates

A number of assumptions were used in designing the model. All deaths were assumed to be from mCRC due to the high mortality risk in this patient population. The rate of death for different treatment regimens was assumed to be constant. Patients could have only one treatment procedure with CRS/HIPEC. Progression with a particular systemic chemotherapy regimen precluded further treatment with that regimen. Intolerance for systemic chemotherapy was the same for all regimens. There were no chemotherapy holidays.

Estimates for disease mortality, probabilities, utilities for different health states, and costs were taken from the literature (Table 1). The rates of disease progression with

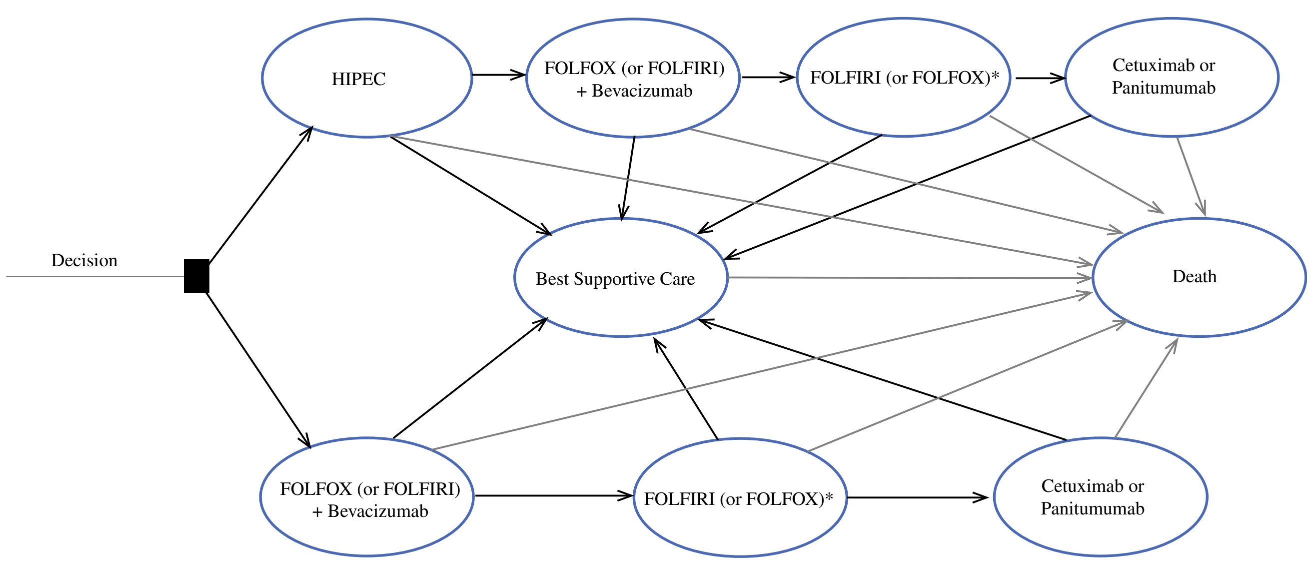

FIG. 1 Markov model of decision tree and different health states for patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) or systemic chemotherapy. *Regimen switch (to FOLFIRI if FOLFOX is used as first-line treatment and to FOLFOX if FOLFIRI is used as first-line treatment). ¶K-RAS wild-type

TABLE 1 Markov model input parameters with ranges and distributions for one-way sensitivity and probabilistic sensitivity analyses

Variable	Base case	Range	Distribution	References
Survival				
Median OS chemo (months)	12.6	12.6–23.9	Log normal	3,6–8
HR for CRS/HIPEC	0.55	0.42–0.55	Log normal	7,28
Complications (%)				
Major post-CRS/HIPEC	33	22.9–42.0	Beta	9,43–45
Chemo	6.5	5–8	–	17
Incomplete resection (%)	20	20–32.2	Beta	6,9,45
Perioperative mortality CRS/HIPEC (%)	8	1.4–8	Beta	6,9,10,43–45
CRS/HIPEC costs ($)[a]				
Direct hospital	39,666	26,793–51,721	Triangular	31,32,46
Clinic visit	53	49–70	–	22
Chemo costs ($ per cycle)[a]				
Administration	399	340–511	–	22
FOLFOX[b]	173	138–216	Triangular	20
FOLFIRI[b]	130	104–163	Triangular	20
Bevacizumab[b]	2989	2391–3736	Triangular	20
Cetuximab[b]	6197	4958–7746	Triangular	20
Panitumumab[b]	5242	4194–6553	Triangular	20
Complication costs ($)[a]				
Major complication after CRS/HIPEC	13,891	11,113–17,364	Triangular	32
Chemo adverse event	2385	1908–2981	Triangular	20
KRAS mutation (%)	43	35.6–43	Beta	19,47
Utility				
Post-CRS/HIPEC disease-free[c,d]	0.79	0.70–0.89	Beta	48
Chemo first-line[d]	0.76	0.73–0.79	Beta	49
Chemo second-line[d]	0.72	0.69–0.75	Beta	50
Chemo third-line[d]	0.68	0.64–0.72	Beta	50
Best supportive care[d]	0.59	0.56–0.62	Beta	51

OS, overall survival; HR, hazard ratio; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

[a]All costs in 2017 U.S. dollars

[b]Drug costs varied ± 20% for sensitivity analysis

[c]Post-HIPEC utility at 6 months

[d]Utilities varied over 95% confidence intervals

first-, second-, and third-line chemotherapy were taken from randomized trials.[17–19]

Drug costs were estimated as the average sale prices from the 2017 Medicare and Medicaid services.[20]

The costs for a 2-weeks cycle of FOLFOX was determined by dosing of a 400-mg/m^2 fluorouracil bolus and a 2400-mg/m^2 infusion during 46 h, 400 mg/m^2 of folinic acid, and 85 mg/m^2 of oxaliplatin. The costs for a 2-weeks cycle of FOLFIRI was determined by dosing of a 400-mg/m^2 fluorouracil bolus and a 2400-mg/m^2 infusion during 46 h, 400 mg/m^2 of folinic acid, and 180 mg/m^2 of irinotecan. The costs for a 2-weeks cycle of bevacizumab was based on 5-mg/kg dosing. The costs for a 2-weeks cycle of cetuximab was based on an initial dose of 400 mg/m^2 and a weekly maintenance dose of 250 mg/m^2. The costs for a 2-weeks cycle of panitumumab was based on 6-mg/kg dosing.

Drug dosing was calculated using a height of 169 cm, a weight of 82.8 kg, and a body surface area of 1.70 m^2. These estimates were based on the body habitus of the average American adult.[21] Chemotherapy administration and clinic visit costs were calculated from the 2017 Medicare physician fee schedule.[22]

Major perioperative complications were defined as either grade 3 or grade 4 according to National Cancer Institute common toxicity criteria or as grade 3 or 4 according to Clavien-Dindo classification.[23] Systemic chemotherapy grade 3 or 4 adverse events included venous thromboembolism (VTE) requiring anti-coagulation. The costs for VTE were calculated as treatment with enoxaparin (dose 1 mg/kg BID) for 6 months.[24] The estimated utility losses for major perioperative complications[25] and chemotherapy adverse events[26] were taken from the literature.

Adjuvant systemic chemotherapy was completed by 31.6% of the patients treated with CRS/HIPEC based on model estimates of performance status and disease progression. Patients with recurrence after CRS/HIPEC were treated with systemic chemotherapy regimens provided they had adequate performance status and did not have intolerance for the particular chemotherapy regimen. The utilities for the patients with recurrence after CRS/HIPEC receiving systemic chemotherapy were the same as those for the patients treated with systemic chemotherapy alone. When specific utilities for the patients treated with CRS/HIPEC were not available from the literature, a conversion from disease-specific HR-QOL evaluations was calculated.[27]

Validation

Internal validation was achieved by comparing the model survival curves with the only published randomized clinical trial comparing CRS/HIPEC with systemic chemotherapy in PC from mCRC.[28] The results of the model closely approximated the clinical trial results (Fig. A1). External validation was achieved by comparing the model survival curves with those for published series of a large cohort.[7]

Sensitivity Analysis

Univariate sensitivity analysis was used for a number of different input parameters in the model to address uncertainty. Ranges of model parameters were taken from the literature. Variances in the utilities of different health states were calculated from 95% confidence intervals. When variances in cost data were not available in the literature, the ranges were calculated as ± 20% of the index price.

A probabilistic sensitivity analysis (PSA) was used to create a robust model that was applicable over a range of model input possibilities (Table 1). Analysis was performed with 100,000 model simulations. An acceptability curve was generated for the different treatment methods over a range of WTP thresholds. The expected value of perfect information (EVPI) was calculated from the PSA. The EVPI represents the additional value that would be gained if the information used for the different parameters in the model were perfect. Generally, a lower EVPI suggests that little value is gained with efforts to quantify parameter inputs more accurately.

RESULTS

Base Case

The results of the base-case analysis are summarized in Table 2. The total cost of treatment for CRS/HIPEC was $64,499 compared with $32,637 for systemic chemotherapy. Treatment with CRS/HIPEC provided 0.86 QALY (1.19 LY), whereas treatment with systemic chemotherapy provided 0.51 QALY (0.76 LY). The ICER for treatment with CRS/HIPEC versus systemic chemotherapy was $91,034 per QALY gained ($74,098 per LY gained). Assuming a WTP of $100,000 per QALY, treatment with CRS/HIPEC would be considered cost-effective.

Univariate Sensitivity Analysis

The tornado diagram in Fig. 2 summarizes the results of the univariate sensitivity analysis of the base case (only parameters with the largest influence in ICER from the base case are shown). The total costs for treatment with CRS/HIPEC had the largest effect on the calculated ICER. The CRS/HIPEC procedure remained a cost-effective treatment within a WTP threshold of $100,000 per QALY for all ranges of input parameters except total cost of CRS/HIPEC, utility after CRS/HIPEC, and proportion of incomplete resections with CRS/HIPEC. Variations in systemic chemotherapy costs including FOLFOX, cetuximab, FOLFIRI (not shown), and panitumumab (not shown) had little effect in terms of change in the ICER calculated from the base case.

Probabilistic Sensitivity Analysis

The PSA for 100,000 model simulations is represented in Fig. 3. Data points falling to the right and below the WTP threshold represent cost-effective strategies. The majority of simulations fell below the cost-effective WTP

TABLE 2 Summary of base-case analysis

Result	Chemo	HIPEC	Incremental
LY	0.76	1.19	0.43
QALY	0.51	0.86	0.35
Total cost ($)	32,637	64,499	
ICER			
$/LY			74,098
$/QALY			91,034

HIPEC hyperthermic intraperitoneal chemotherapy; *LY* life-years; *QALY* quality-adjusted life-year; *ICER* incremental cost-effectiveness ratio

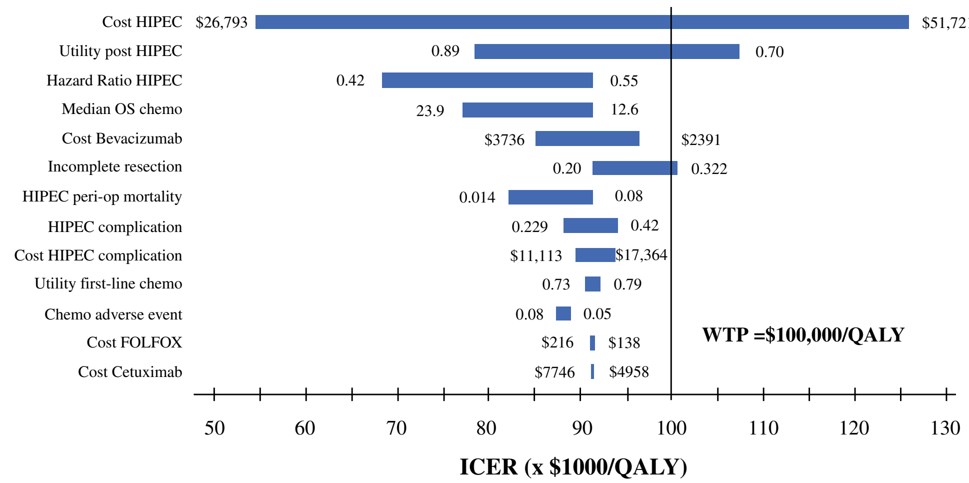

FIG. 2 Tornado diagram of univariate sensitivity analysis for the base case

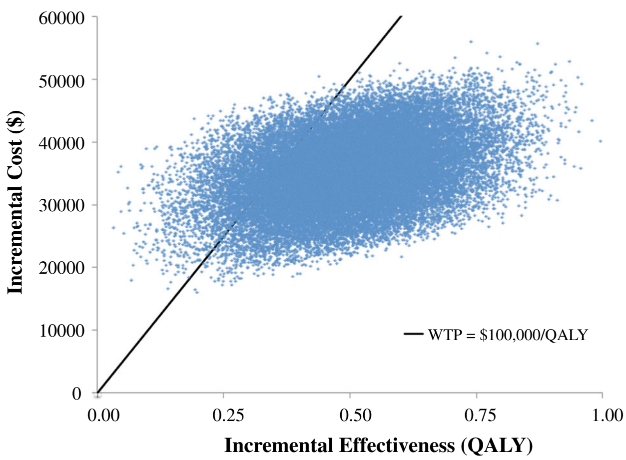

FIG. 3 Incremental cost and effectiveness calculation from probabilistic sensitivity analysis performed for more than 100,000 model case simulations

threshold. The average cost of the model simulations for the CRS/HIPEC treatment strategy was $71,799 for 1.13 QALY gained in effectiveness.

For the systemic chemotherapy strategy, the average cost was $36,566 for 0.64 QALY gained in effectiveness. This translated to an ICER of $70,807 per QALY gained based on the average costs and effectiveness from the PSA simulations. The cost-effectiveness acceptability curve summarizes the two strategies among varying WTP thresholds (Fig. A2). The likelihood of CRS/HIPEC being a cost-effective strategy at a WTP threshold of $100,000 per QALY was 87%. The expected value of perfect information was $796 per person at a WTP threshold of $100,000 per QALY (Fig. A3).

DISCUSSION

We performed a cost-effectiveness analysis of CRS/HIPEC compared with systemic chemotherapy as the primary treatment for patients with isolated PC from mCRC. This demonstrated the cost-effectiveness of treatment with CRS/HIPEC versus systemic chemotherapy, with an ICER of $91,034 per QALY gained ($74,098 per LY gained) for the base-case model. The 100,000 model simulations in the PSA also demonstrated cost-effectiveness, with an ICER of $70,807 per QALY gained. To the best of our knowledge, this is the first cost-effectiveness analysis to evaluate CRS/HIPEC in the United States using a Markov model.[16]

A number of studies have performed cost analysis of CRS/HIPEC in different countries.[29–33] However, results included treatment for a number of different peritoneal surface malignancies and were not specific to mCRC. Two studies specifically evaluated the cost-effectiveness of CRS/HIPEC for the treatment of PC from mCRC.[14,15] In the first study, Bonastre et al.[14] evaluated 96 patients who had PC from mCRC treated with either CRS/HIPEC or palliative chemotherapy between 1998 and 2003 in France. During the 3-years observation period, treatment with CRS/HIPEC yielded a survival gain of 8.3 months for an additional cost of €58,086. This translates to an ICER of €83,980 per LY gained. However, this study was performed in the era of fluorouracil-leucovorin systemic chemotherapy regimens.

In the second study, Chua et al.[15] evaluated 136 patients who had a number of different peritoneal surface malignancies treated with CRS/HIPEC between 2002 and 2008 in Australia. Included in the cohort were 34 patients with mCRC. The estimated ICER for those who had mCRC treated with CRS/HIPEC was Australian Dollars (AUD) $66,148 per LY gained. Within the limitations of comparing cost-effectiveness across different countries and health care systems, our results are consistent with the current literature.

One advantage of our study was its report of cost-effectiveness in cost per QALY, which translates across different diseases and can assist in making health care policy decisions.

The CRS/HIPEC treatment is used increasingly for the treatment of different peritoneal surface malignancies in the United States. In the context of emerging therapies in oncology and increasing health care costs for new treatments, health economics evaluations are critical concerning a high value of care achieved per dollar spent.[34] This highlights the importance of the current study demonstrating the cost-effectiveness of CRS/HIPEC in mCRC.

As with any cost-effectiveness evaluation, this study had a number of limitations. Only one randomized control trial has evaluated CRS/HIPEC versus systemic chemotherapy in the treatment of PC from mCRC,[6] and this served as the basis of our model. This trial has been criticized because it was conducted in the era of fluorouracil-leucovorin systemic chemotherapy and included some patients with appendiceal adenocarcinoma, which portends a more favorable prognosis than mCRC. However, the univariate sensitivity and PSA in this study incorporated a range of survival outcomes from prospective evaluations in the context of current chemotherapy regimens to account for this limitation. The model demonstrated good internal validation by closely approximating the clinical trial results. The external validation less closely approximated the literature, but these results were based on cohort series that may have had selection bias in the allocation of patients in chemotherapy or CRS/HIPEC treatments.

The model implemented for this evaluation was an oversimplification of the current systemic chemotherapy options for treatment of mCRC,[35] Emerging treatments, including immunotherapies,[36] were not included in this analysis. However, because this treatment currently is limited to a small percentage of patients who are microsatellite instability-high, it is less likely to have a significant impact on the overall findings. The model also was an oversimplification of treatment in the CRS/HIPEC arm of the study. The patients in the model can be treated with CRS/HIPEC only once, whereas in practice, some patients may have additional procedures.[9,37] In contrast to the randomized trial by Verwaal et al.,[6] many patients treated with CRS/HIPEC may receive neoadjuvant systemic chemotherapy. Although this represents a potential increase in cost of the overall CRS/HIPEC treatment, there could be an associated reduction in the proportion of incomplete resections because those with progressive disease or less favorable biology would not proceed to CRS/HIPEC.

The estimation of utilities is important in determining the cost-effectiveness of any treatment. Although we accounted for the utility loss from a major perioperative complication after CRS/HIPEC, this could be a conservative estimate because some have reported that HR-QOL for patients with major complications recovers and is similar to those for patients without major complications.[38]

A WTP threshold of $100,000 per QALY gained was chosen for this study, consistent with previous reports of cost-effective strategies.[39] This may be a conservative estimate because some studies have suggested that a WTP threshold range of $109,000 to $183,000 per QALY may be appropriate based on current societal preferences in the United States.[40]

The costs of adverse events from febrile neutropenia for patients treated with systemic chemotherapy were not included in the analysis. Although the incidence of grade 3 or 4 toxicity due to febrile neutropenia from FOLFOX/FOLFIRI-based regiments is limited,[18] this could be a potential limitation of the study. This likely suggests that the current study offers a more conservative estimate of the cost-effectiveness of CRS/HIPEC.

Recently, the results of the Partinariat de Reserche en Oncologie Digestive (PRODIGE)-7 trial demonstrated acceptable results from CRS alone for isolated PC from mCRC, particularly for patients with low-volume disease.[41] A median overall survival period of 41.2 months for CRS and 41.7 months for CRS/HIPEC are promising and fall within the parameters of the probabilistic sensitivity analysis of the current model.

Although the results of this health economic evaluation are encouraging, showing that CRS/HIPEC is a cost-effective treatment option for isolated PC from mCRC, it should be emphasized that this treatment option is not beneficial for all patients with PC from mCRC. The decision to proceed with CRS/HIPEC should be based on a multi-disciplinary discussion with considerations for age, comorbidities, extent of tumor burden, disease-free interval, histology, and functional status.[42]

This study demonstrated an acceptable increased cost-effectiveness ratio for the treatment of isolated PC from mCRC with CRS/HIPEC in the United States. This information should be useful for health economic policy decisions in the future.

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9–29. https://doi.org/10.3322/caac.21208.
2. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. *Br J Surg*. 2002;89:1545–50. https://doi.org/10.1046/j.1365-2168.2002.02274.x.
3. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of North Central Cancer Treatment Group phase III trials N9741 and N9841. *J Clin Oncol*. 2012;30:263–7. https://doi.org/10.1200/jco.2011.37.1039.

4. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol*. 2011;22:1535–46. https://doi.org/10.1093/annonc/mdq632.
5. Van Cutsem E, Kohne C-H, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408–17.
6. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol*. 2003;21:3737–43. https://doi.org/10.1200/jco.2003.04.187.
7. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ III. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. *Cancer*. 2010;116:3756–62. https://doi.org/10.1002/cncr.25116.
8. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol*. 2009;27:681–5. https://doi.org/10.1200/jco.2008.19.7160.
9. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004;22:3284–92. https://doi.org/10.1200/jco.2004.10.012.
10. Bijelic L, Yan TD, Sugarbaker PH. Treatment failure following complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from colorectal or appendiceal mucinous neoplasms. *J Surg Oncol*. 2008;98:295–9. https://doi.org/10.1002/jso.21084.
11. Turaga K, Levine E, Barone R, et al. Consensus guidelines from the American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol*. 2013;21:1501–5. https://doi.org/10.1245/s10434-013-3061-z.
12. Chua TC, Esquivel J, Pelz JOW, Morris DL. Summary of current therapeutic options for peritoneal metastases from colorectal cancer. *J Surg Oncol*. 2013;107:566–73. https://doi.org/10.1002/jso.23189.
13. Esquivel J, Piso P, Verwaal V, et al. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer. *J Surg Oncol*. 2014;110:777–8. https://doi.org/10.1002/jso.23722.
14. Bonastre J, Chevalier J, Elias D, et al. Cost-effectiveness of intraperitoneal chemohyperthermia in the treatment of peritoneal carcinomatosis from colorectal cancer. *Value Health*. 2008;11:347–53. https://doi.org/10.1111/j.1524-4733.2007.00249.x.
15. Chua TC, Martin S, Saxena A, et al. Evaluation of the cost-effectiveness of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (peritonectomy) at the St George Hospital Peritoneal Surface Malignancy Program. *Ann Surg*. 2010;251:323–9. https://doi.org/10.1097/sla.0b013e3181c9b53c.
16. Vanounou T, Garfinkle R. Evaluation of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin in the era of value-based medicine. *Ann Surg Oncol*. 2016;23:2556–61. https://doi.org/10.1245/s10434-016-5096-4.
17. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26:2013–9. https://doi.org/10.1200/jco.2007.14.9930.
18. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229–37. https://doi.org/10.1200/jco.2004.05.113.
19. Karapetis C, Khambata-Ford S, Jonker D, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359:1757–65.
20. Centers for Medicare and Medicaid Services. 2017. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Federal-Regulation-Notices-Items/CMS-1654-F.html. Accessed 25 Feb 2018.
21. Centers for Disease Control and Prevention. 2017. https://www.cdc.gov/nchs/fastats/body-measurementshtm. Accessed 25 Feb 2018.
22. Centers for Medicare and Medicaid Services. 2017. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/. Accessed 25 Feb 2018.
23. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. *Ann Surg*. 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
24. Lyman GH, Bohlke K, Falanga A. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *JOP*. 2015;11:e442–4. https://doi.org/10.1200/jop.2015.004473.
25. Dodson RM, McQuellon RP, Mogal HD, et al. Quality-of-life evaluation after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2016;23:772–83. https://doi.org/10.1245/s10434-016-5547-y.
26. Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. *Ann Emerg Med*. 2010;56:321–32. https://doi.org/10.1016/j.annemergmed.2010.03.029.
27. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient-level data are not available). *Value Health*. 2008;11:1131–43. https://doi.org/10.1111/j.1524-4733.2008.00352.x.
28. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-Year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2008;15:2426–32. https://doi.org/10.1245/s10434-008-9966-2.
29. Pietro F Bagnoli, Cananzi FCM, Brocchi A, et al. Peritonectomy and hyperthermic intraperitoneal chemotherapy: cost analysis and sustainability. *Eur J Surg Oncol*. 2015;41:386–91. https://doi.org/10.1016/j.ejso.2014.12.004.
30. Baratti D, Scivales A, Balestra MR, et al. Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol*. 2010;36:463–9. https://doi.org/10.1016/j.ejso.2010.03.005.
31. Naffouje SA, O'Donoghue C, Salti GI. Evaluation of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a community setting: a cost-utility analysis of a hospital's initial experience and reflections on the health care system. *J Surg Oncol*. 2016;113:544–7. https://doi.org/10.1002/jso.24162.
32. Squires MH, Staley CA, Knechtle W, et al. Association between hospital finances, payer mix, and complications after hyperthermic intraperitoneal chemotherapy: deficiencies in the current healthcare reimbursement system and future implications. *Ann Surg Oncol*. 2015;22:1739–45. https://doi.org/10.1245/s10434-014-4025-7.

33. Tentes AA, Pallas N, Korakianitis O, et al. The cost of cytoreductive surgery and perioperative intraperitoneal chemotherapy in the treatment of peritoneal malignancy in one Greek institute. *J BUON*. 2012;17:776–80.
34. Porter ME. What is value in health care? *N Engl J Med*. 2010;363:2477–81.
35. *NCCN Guidelines–Colon Cancer*. Plymouth Meeting, PA: Harborside Press; 2017. pp. 1–143.
36. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182–91. https://doi.org/10.1016/s1470-2045(17)30422-9.
37. Klaver YLB, Chua TC, Verwaal VJ, de Hingh IHJT, Morris DL. Secondary cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal recurrence of colorectal and appendiceal peritoneal carcinomatosis following prior primary cytoreduction. *J Surg Oncol*. 2013;107:585–90. https://doi.org/10.1002/jso.23303.
38. Hamilton TD, Taylor EL, Cannell AJ, McCart JA. Impact of major complications on patients' quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2016;23:2946–52. https://doi.org/10.1245/s10434-016-5231-2.
39. Weinstein M, Skinner J. Comparitive effectiveness and health care spending: implications for reform. *N Engl J Med*. 2010;362:460–5.
40. Braithwaite RS, Meltzer DO, King JT, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care*. 2008;46:349–56.
41. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol*. 2018;36(18 Suppl):3503. https://doi.org/10.1200/jco.2018.36.18_suppl.lba3503.
42. Esquivel J, Lowy AM, Markman M, et al. The American Society of Peritoneal Surface Malignancies (ASPSM) multiinstitution evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1013 Patients with colorectal cancer with peritoneal carcinomatosis. *Ann Surg Oncol*. 2014;21:4195–201. https://doi.org/10.1245/s10434-014-3798-z.
43. Jafari MD, Halabi WJ, Stamos MJ, et al. Surgical outcomes of hyperthermic intraperitoneal chemotherapy. *JAMA Surg*. 2014;149:170–6. https://doi.org/10.1001/jamasurg.2013.3640.
44. Shen P, Thai K, Stewart JH, et al. Peritoneal surface disease from colorectal cancer: comparison with the hepatic metastases surgical paradigm in optimally resected patients. *Ann Surg Oncol*. 2008;15:3422–32. https://doi.org/10.1245/s10434-008-0127-4.
45. Kianmanesh R, Scaringi S, Sabate J-M, et al. Iterative cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis of colorectal origin with or without liver metastases. *Ann Surg*. 2007;245:597–603. https://doi.org/10.1097/01.sla.0000255561.87771.11.
46. Hinkle NM, MacDonald J, Sharpe JP, Dickson P, Deneve J, Munene G. Cytoreduction with hyperthermic intraperitoneal chemotherapy: an appraisal of outcomes and cost at a newly established peritoneal malignancy program. *Am J Surg*. 2016;212:413–8. https://doi.org/10.1016/j.amjsurg.2016.01.022.
47. Amado RG, Wolf M, Peeters M, et al. Wild-type KRASIs required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:1626–34. https://doi.org/10.1200/jco.2007.14.7116.
48. McQuellon RP, Danhauer SC, Russell GB, et al. Monitoring health outcomes following cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol*. 2007;14:1105–13. https://doi.org/10.1245/s10434-006-9304-5.
49. Bennett L, Zhao Z, Barber B, et al. Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. *Br J Cancer*. 2011;105:1495–502. https://doi.org/10.1038/bjc.2011.409.
50. Odom D, Barber B, Bennett L, et al. Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with panitumumab. *Int J Colorectal Dis*. 2011;26:173–81. https://doi.org/10.1007/s00384-010-1112-5.
51. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *The Lancet*. 2013;381:303–12. https://doi.org/10.1016/s0140-6736(12)61900-x.