Early Cost-effectiveness Analysis of Risk-Based Selection Strategies for Adjuvant Treatment in Stage II Colon Cancer: The Potential Value of Prognostic Molecular Markers

Gabrielle Jongeneel[1], Marjolein J.E. Greuter[1], Natalia Kunst[1,2,3,4], Felice N. van Erning[5], Miriam Koopman[6], Jan P. Medema[7,8], Louis Vermeulen[7,8], Jan N.M. Ijzermans[9], Geraldine R. Vink[5,6], Cornelis J.A. Punt[10], and Veerle M.H. Coupé[1]

ABSTRACT

Background: To explore the potential value of consensus molecular subtypes (CMS) in stage II colon cancer treatment selection, we carried out an early cost-effectiveness assessment of a CMS-based strategy for adjuvant chemotherapy.

Methods: We used a Markov cohort model to evaluate three selection strategies: (i) the Dutch guideline strategy (MSS+pT4), (ii) the mutation-based strategy (MSS plus a BRAF and/or KRAS mutation or MSS plus pT4), and (iii) the CMS-based strategy (CMS4 or pT4). Outcomes were number of colon cancer deaths per 1,000 patients, total discounted costs per patient (pp), and quality-adjusted life-years (QALY) pp. The analyses were conducted from a Dutch societal perspective. The robustness of model predictions was assessed in sensitivity analyses. To evaluate the value of future research, we performed a value of information (VOI) analysis.

Results: The Dutch guideline strategy resulted in 8.10 QALYs pp and total costs of €23,660 pp. The CMS-based and mutation-based strategies were more effective and more costly, with 8.12 and 8.13 QALYs pp and €24,643 and €24,542 pp, respectively. Assuming a threshold of €50,000/QALY, the mutation-based strategy was considered as the optimal strategy in an incremental analysis. However, the VOI analysis showed substantial decision uncertainty driven by the molecular markers (expected value of partial perfect information: €18M).

Conclusions: On the basis of current evidence, our analyses suggest that the mutation-based selection strategy would be the best use of resources. However, the extensive decision uncertainty for the molecular markers does not allow selection of an optimal strategy at present.

Impact: Future research is needed to eliminate decision uncertainty driven by molecular markers.

Introduction

After curative surgery, stage II patients with colon cancer have a 15% to 20% risk to develop a recurrence (1–3). This risk may be reduced by treatment with adjuvant chemotherapy. However, to prevent unnecessary exposure to potentially toxic treatment in patients who have already been cured by surgery alone, only stage II patients with a high risk of recurrence should be eligible for chemotherapy. The Dutch guidelines currently recommend to prescribe adjuvant chemotherapy only for stage II patients with microsatellite stable (MSS) pT4 tumors (4). However, insight into the molecular heterogeneity of tumors is increasing (5–7). Additional molecular markers, with an impact on either prognosis or response to adjuvant treatment, could potentially improve the currently used high-risk classification of patients with stage II colon cancer (5, 8).

In a recent model-based cost-effectiveness study, we showed that adding BRAF and/or KRAS mutation status as a selection criterion for adjuvant chemotherapy in stage II colon cancer can potentially improve patients' survival (9). In addition to BRAF and KRAS mutation status, the prognostic value of a large number of other molecular markers in the stage II colon cancer population has been demonstrated (5, 8). To take the interconnectivity between these markers into account, the consensus molecular subtypes (CMS) for colorectal cancer were introduced (7). The CMS classification distinguishes four subtypes of specific molecular markers: CMS1 (MSI immune), CMS2 (canonical), CMS3 (metabolic), and CMS4 (mesenchymal; ref. 7). A pooled analysis of 1,785 patients with stage I to IV colorectal cancer showed that patients with a CMS4 classification have a worse prognosis in terms of disease-free survival compared with patients with CMS1 [HR: 1.77; 95% confidence interval (CI), 1.34–2.34], CMS2 (HR: 1.70; 95% CI, 1.39–2.06), and CMS3 (HR: 1.74; 95% CI, 1.29–2.33). Given the prognostic character, the CMS classification was discussed by several studies as a promising feature to inform adjuvant treatment decisions in stage II colon cancer (7, 10, 11).

[1]Department of Epidemiology and Data Science, Amsterdam UMC, VU University, Amsterdam, the Netherlands. [2]Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston, Massachusetts. [3]Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center, Yale University School of Medicine, New Haven, Connecticut. [4]Public Health Modeling Unit, Yale University School of Public Health, New Haven, Connecticut. [5]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands. [6]University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [7]Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Center for Experimental Molecular Medicine (CEMM), Amsterdam, the Netherlands. [8]Oncode Institute, Amsterdam, the Netherlands. [9]Department of General Surgery, Erasmus MC University Medical Center, Rotterdam, the Netherlands. [10]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Gabrielle Jongeneel, Department of Epidemiology and Biostatistics, Amsterdam University Medical Centers, Amsterdam, 1081HV Amsterdam, the Netherlands. E-mail: g.jongeneel@amsterdamumc.nl

Cancer Epidemiol Biomarkers Prev 2021;30:1726–34

doi: 10.1158/1055-9965.EPI-21-0078

However, limited survival data for CMS is available in the stage II population, since the classification system is only introduced in 2015.

In this study, we aimed to explore the potential value of using the prognostic information of CMS in stage II colon cancer treatment selection and to provide insight into the value of additional prospective research for the Dutch stage II colon cancer population by means of an early cost-effectiveness assessment. Using the Personalized Adjuvant TreaTment in EaRly stage coloN cancer (PATTERN) model (12), we compared health effects and costs of three selection strategies to allocate chemotherapy in the stage II colon cancer population: (i) the current Dutch guideline strategy, (ii) a mutation-based selection strategy, and (iii) a CMS-based strategy. We performed a number of sensitivity analyses to examine the robustness of the results. Furthermore, we evaluated decision uncertainty in our cost-effectiveness assessment using a value of information (VOI) analysis.

Materials and Methods

PATTERN model

The PATTERN model has been comprehensively described elsewhere (12). The flowchart of the model is shown in Supplementary Fig. S1 and the model parameters are reported in Supplementary Table S1. In short, the PATTERN model is a Markov cohort model with five health states: diagnosis, recurrence, 90-day mortality, death of other causes, and death due to colon cancer. We used the Netherlands Cancer Registry (NCR) data for model parametrization ($n = 2{,}271$; ref. 13). Only patients without adjuvant treatment were selected for model quantification. As an additional step, an HR for treatment effect was included in the transition from diagnosis to recurrence, based on pooled trial data (Supplementary Table S1; ref. 14). The PATTERN model distinguishes 72 clinical and/or pathologic subgroups for pT stage, tumor sidedness, number of evaluated lymph nodes, and age, which were weighted such that the distribution of clinical and pathologic features reflects the Dutch stage II colon cancer population (Supplementary Methods and Materials). The PATTERN model was extensively validated, both internally and externally (12).

Inclusion of mutation status in the PATTERN model

Data of three cohorts ($n = 334$) were used to distinguish between three biomarker subgroups in the PATTERN model: (i) microsatellite instable tumors (MSI), independent of BRAF and KRAS mutation status, (ii) MSS tumors without a mutation for BRAF or KRAS (MSSdwt), and (iii) MSS in combination with a mutation in BRAF and/or KRAS (MSSmut; refs. 15, 16). The prognostic impact of biomarker status was incorporated in the model by means of an HR affecting the transition from diagnosis to recurrence. These HRs were estimated to be 0.25, 0.88, and 1.53 for the MSI, MSSdwt, and MSSmut subgroups compared with the general stage II colon cancer population, respectively (Supplementary Table S1; ref. 12). A detailed description of how we estimated and incorporated these HRs in the PATTERN model is described elsewhere (12).

Inclusion of CMS in the PATTERN model

To include estimates for the prognostic impact of CMS subgroups in the PATTERN model, we used patient-level data of 428 patients with stage II colorectal cancer that were included in the pooled analysis of Guinney and colleagues (2015), which focused on the optimal classification of CMS (7, 17–21). Baseline characteristics for included patients are shown in Supplementary Table S2. The average age was 67.1 years. The majority of the patients had a CMS2 classification (45.6%), followed by CMS4 (23.1%), CMS1 (18.2%), and CMS3 (13.1%). Eighty-four recurrences (19.6%) were observed within an average follow-up time of 51 months (range: 1–201 months). As the disease-free-survival in patients with CMS1, CMS2, and CMS3 was comparable (Supplementary Fig. S2), we distinguished two CMS subgroups in the PATTERN model: CMS1–3 and CMS4 (Supplementary Methods and Materials). To incorporate CMS classification in the PATTERN model, the time-to-event model reflecting the transition from diagnosis to recurrence was adjusted by including HRs of 0.80 and 1.70 for CMS1to CMS3 and CMS4, respectively compared with the general stage II population (Supplementary Table S1; ref. 12).

Strategies

Three strategies were evaluated. First, we evaluated a strategy that represented the current Dutch guideline recommendations. In this strategy, patients with a MSS status AND a pT4 stage receive adjuvant chemotherapy (Dutch guideline strategy). Second, a strategy was evaluated in which patients with a MSS status combined with a mutation in BRAF and/or KRAS OR a MSS status combined with a pT4 stage receive adjuvant chemotherapy (mutation strategy; ref. 22). In the third strategy, patients with a CMS4 classification or a pT4 stage receive adjuvant chemotherapy (CMS strategy). Note that these strategies were solely based on the prognostic value of the MMR, BRAF, KRAS, and CMS parameters (Supplementary Table S3). For all strategies we assumed adherence as observed in 2018 to 2019 NCR data. That is, 44% of the high-risk patients ages <75 received chemotherapy and 11% of the high-risk patients ages ≥75 received chemotherapy. In accordance with the Dutch guidelines, patients were treated with 3 months of capecitabine plus oxaliplatin (CAPOX).

Costs

We present an overview of resource use, costs, and utilities in **Table 1**. Costs were determined from a societal perspective and included costs for initial surgery, mutation testing, gene expression profiling, drug costs, costs of managing adverse events, absenteeism from work, patient's travel to the hospital, surveillance, and treatment for recurrence of disease (4, 22–30). Surveillance was based on the recommendations in the Dutch guideline (4), that is, a carcinoembryonal antigen (CEA) determination every 6 months and an ultrasound scan or CT scan of the liver once a year during the first 5 years after surgery. In addition, patients undergo colonoscopy every 3 years, with the first colonoscopy one year after surgery.

Health utilities

Health utilities were estimated using data from the Prospective Dutch ColoRectal Cancer cohort (PLCRC; ref. 31). For the present study, we selected 859 participants who were diagnosed with stage II or III CC between 2011 and 2019 and completed the EQ-5D-5L (32, 33). The patients' scores on this quality-of-life questionnaire were summarized into a health utility score using the Dutch tariff (34).

To inform the PATTERN model, average health utilities were calculated for different time periods in the disease process, separately for patients with and without adjuvant chemotherapy (33). A full overview of the estimated utilities for each time period is provided in **Table 1**.

Base-case analysis

Model predictions were conducted from a societal perspective, using a lifelong time horizon. The outcomes included the number of recurrences and deaths due to colon cancer per 1,000 patients, life years per patient (pp), quality-adjusted life years (QALYs) pp, total life-time costs pp, and net monetary benefit (NMB) associated with each

Table 1. Overview of resource use, costs, and utilities.

Costs[a]	Value	Proportion	Reference
Initial surgery	€13,576[b]		(28)
Biomarker tissue test			
MMR	€64		(28)
BRAF and KRAS mutation status	€65		(30)
Gene expression profiling	€500		Expert opinion
Treatment cost per full regimen			
CAPOX[c]	€5,925		(4, 22, 26)
% quitting before end regimen		0.25	(23)
Adverse event cost per case[d]			
Grade 3/4 neutropenia	€99		(22, 26, 50)
Febrile neutropenia	€3,459		(22, 26, 50)
Grade 3/4 diarrhea	€50		(22, 26, 50)
Absenteeism costs per cycle[e]			(26)
<55	€5,569		
55–65	€5,164		
Travel costs per cycle	€9		(26)
Surveillance costs[f]			
Colonoscopy	€888		(4, 26)
Colonoscopy with complications	€1,494	0.028	(27)
Ultrasound scan	€87		(4, 26)
CEA determination	€8		(4, 28)
Relapse costs	€45,485		(29)
Utilities[g]	**No adjuvant treatment**	**Adjuvant treatment**	
Before surgery (month 1)	0.85	0.85	(31, 33)
After surgery/before chemotherapy (month 2–3)	0.85	0.81	(31, 32)
During chemotherapy (month 4–6)	0.86	0.83	(31, 32)
First year after chemotherapy (month 7–18)	0.86	0.83	(31, 33)
More than 12 months after chemotherapy	0.83	0.83	(31, 33)
Recurrence (month 1–60 after recurrence)	0.45	0.45	(51–53)

Note: All costs were standardized to 2020 Euros, using the consumer price index (49).
[a]The cost parameters were randomly assigned in the probabilistic sensitivity analysis using a normal distribution.
[b]DBC tariffs from 24 hospitals in the Netherlands were averaged.
[c]The treatment with CAPOX consisted of 4 cycles of 3 weeks (4).
[d]The TOSCA trial was used to determine the adverse event rates (50). Costs were based on follow-up care per adverse event category. For neutropenia follow-up, care was defined as a visit to the outpatient clinic, for febrile neutropenia as a hospital stay of 5 days, and for diarrhea as oral rehydration medication (22, 26).
[e]To calculate the absenteeism costs, we assumed that (i) the male-to-female ratio was 0.47/0.53 (13); (ii) number of hours worked per week was 40 and 38 for men and 28 and 25 for women in the age groups <55 and 55–65, respectively (49); and (iii) patients do not work during chemotherapy. The absenteeism costs were calculated according to the friction cost approach.
[f]Surveillance costs were calculated according to the Dutch guideline for colon cancer surveillance.
[g]The utility parameters were randomly assigned in the probabilistic sensitivity analysis using a beta distribution.

strategy. The NMB was calculated for each strategy as: total QALYs × willingness-to-pay threshold – total cost, using a threshold of €50,000/QALY. Dutch discount rates of 1.5% and 4% were used for health effects and costs, respectively (26). We conducted an incremental cost-effectiveness analysis in which the evaluated strategies were ordered from lowest to highest costs. Subsequently, incremental cost-effectiveness ratios (ICER) were calculated between successive non-dominated strategies. The strategy associated with the highest ICER below a willingness-to-pay threshold of €50,000 per QALY was considered the cost-effective strategy (35).

One-way sensitivity analyses

To evaluate the impact of uncertainty on our model predictions, we conducted two one-way sensitivity analyses. First, we increased and decreased the risk to develop a recurrence with 10% in the CMS4 group. Note that the risk of a recurrence in the CMS1 to CMS3 group increased/decreased as well to maintain the same average recurrence risk in the population. Second, we increased and decreased the risk to develop a recurrence with 10% in the MSSmut group. Note that the recurrence risk for the MSI and MSSdwt increased/decreased as well to maintain the same average recurrence risk in the population.

Threshold analysis

Because of rapid developments in the field of genetic testing, the price of a test to determine CMS may likely decrease in the coming years (30). Therefore, we conducted a threshold analysis in which we decreased the costs for determining CMS from €500 in the base-case analysis to €0 in steps of €100. Subsequently, we compared the NMBs for the CMS strategy to the NMB for the mutation strategy to evaluate if the costs for CMS classification would influence the cost-effectiveness ordering of strategies.

Scenario analysis

In the base-case analysis, we focused completely on the prognostic value of the MMR, BRAF, KRAS, and CMS parameters. However, some studies indicated that patients with a CMS4 classification may be resistant to adjuvant chemotherapy (36–38). To investigate the influence of this potential resistance on optimal treatment selection for

patients with stage II colon cancer, we evaluated a scenario in which we assumed that treatment has no effect in patients with a CMS4 classification. Since prescribing adjuvant treatment to patients with CMS4 would be useless without any benefit of the treatment, the CMS strategy was not included in this scenario analysis. Instead, we defined two strategies in which we used the CMS4 classification as feature to exclude patients from adjuvant chemotherapy. The following four strategies were evaluated in this scenario analysis: (i) The Dutch guideline strategy, (ii) the mutation strategy, (iii) a strategy in which patients with MSS and pT4 receive chemotherapy, unless a patient is classified as CMS4 (Dutch guideline strategy without CMS4), (iv) a strategy in which patients with MSS status in combination with a mutation in BRAF and/or KRAS OR pT4 receive chemotherapy, unless the patient is classified as CMS4 (mutation strategy without CMS4).

In line with the base-case analysis, a patients' CMS status was not determined in strategy 1 and 2. That is, part of the patients which were selected for adjuvant chemotherapy in these strategies have a CMS4 classification. We assumed no treatment effect for those patients with a CMS4 classification in the evaluation of strategies 1 and 2, which is the HR for treatment was set to 1 (Supplementary S2; Supplementary Table S6). Subsequently, we adjusted the treatment effect for the other subgroups to 0.65, so that the weighted mean was in line with the treatment effect of 0.73, which was the estimate for the general stage II population (14). In strategy 3 and 4, the CMS status of the patient was determined, so that we were able to exclude patients with a CMS4 classification from adjuvant chemotherapy. Note that for patients that were selected for adjuvant chemotherapy in strategy 3 and 4, also the adjusted treatment effect of 0.65 was applied.

Probabilistic analysis

To estimate the joint impact of uncertainty in all model parameters on model predictions for the three selection strategies evaluated in the base-case analysis, a probabilistic analysis with 1,000 iterations was conducted. The parameters in the PATTERN model were varied simultaneously according to their most appropriate distribution (**Table 1**; Supplementary Table S1). More detailed information about the probabilistic analysis is given in Supplementary Methods and Materials. To visually illustrate the results of the probabilistic analysis, a cost-effectiveness acceptability curve (CEAC) was constructed for a range of willingness-to-pay thresholds (€0-€100,000) per QALY. A CEAC depicts the probability for each strategy to result in the highest NMB at a specific willingness-to-pay threshold. Furthermore, the results of the probabilistic analysis were depicted in cost-effectiveness planes.

The expected value of (partial) perfect information

A VOI analysis provides insight in the decision uncertainty in the evaluation based on currently available evidence. The expected value of perfect information (EVPI) quantifies the value of eliminating uncertainty from all parameters included in the model, and reflects the maximum value that decision makers should be willing to pay for future research (39, 40). The expected value of perfect parameter information (EVPPI) quantifies the value of reducing decision uncertainty by eliminating uncertainty from one parameter or a group of parameters (39). The EVPPI helps to identify drivers of decision uncertainty and to select the potential outcomes that should be targeted in future research. To inform policy makers on the value of future research focusing specifically on an assessment of the prognostic value of genetic features in the stage II CC population, we examined the EVPPI for three sets of parameters: (i) CMS parameters; (ii) MMR,

Table 2. Base-case results of the cost-effectiveness analysis.

	% treated	Colon cancer burden[a]		LY per patient (years)		QALYs per patient (years)		Costs per patient (€)		NMB[b]	ICER in €/QALY
		Recurrences	Deaths	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted		
Dutch guideline strategy	3.2%	162	137	11.18	9.83	9.21	8.10	24,422	23,660	381,183	*reference*
Mutation strategy	13.2%	157	133	11.22	9.87	9.25	8.13	25,297	24,542	381,827	*28,893*
CMS strategy	10.0%	158	134	11.21	9.86	9.24	8.12	25,993	24,643	381,406	*dominated*

Abbreviations: LY, life years; NMB, net monetary benefit.
[a]Total during the lifetime of a cohort of 1,000 patients.
[b]At a willingness-to-pay of €50,000/QALY.

BRAF, and KRAS parameters; and (iii) CMS, MMR, BRAF, and KRAS parameters. As recommended by Rothery and colleagues, we extrapolated our VOI results to a population level using an annual incidence of 3,225 newly diagnosed patients with stage II colon cancer in the Netherlands (1, 39). Furthermore, we assumed a 10-year decision horizon in our VOI analyses. We estimated the EVPI and EVPPI using the Sheffield Accelerated Value of Information (SAVI) tool, which uses a non-parametric regression approach to estimate the EV(P)PI (41).

Results

Effectiveness

For the current Dutch guideline strategy, the model predicted 162 CC recurrences and 137 CC deaths per 1,000 patients (**Table 2**). The CMS strategy and mutation strategy were more effective compared with the Dutch guideline strategy with a decrease of 2.5% and 3.1% in the number of recurrences and 2.2% and 2.9% in CC mortality, respectively. The Dutch guideline strategy resulted in the lowest predicted QALYs of 8.10 pp, followed by the CMS strategy with 8.12 QALYs pp, and the mutation strategy with the highest number of predicted QALYs of 8.13 pp.

Cost-effectiveness

The predicted costs were with €23,660 pp lowest in the current Dutch guideline strategy (**Table 2**). The costs associated with the CMS strategy and with the mutation strategy were higher with €24,643 and €24,542 pp, respectively. The main cost driver in all three strategies was the cost for the initial surgery (Supplementary Table S4). The highest NMB at a willingness-to-pay threshold of 50,000 €/QALY was found for the mutation strategy (€381,827), indicating that this strategy was the preferred strategy at this threshold.

In the incremental cost-effectiveness analysis, the current Dutch guideline strategy served as the first comparator, due to the lowest predicted cost for this strategy (**Table 2**). The mutation strategy was associated with an ICER of 28,893 €/QALY, and represented a cost-effective strategy at a willingness-to-pay threshold of €50,000/QALY (**Fig. 1**). The CMS strategy was dominated by the mutation strategy as the mutation strategy predicted higher QALYs and lower costs compared with the CMS strategy.

One-way sensitivity analyses

Results of the one-way sensitivity analyses are shown in Supplementary Table S5. Increasing/decreasing the recurrence risk in the MSSmut group and decreasing the recurrence risk in the CMS4 group led to comparable ICERs and the same optimal strategy as in the base-case analysis.

When the recurrence risk in the CMS4 group was increased, the CMS strategy was no longer dominated by the mutation strategy and resulted in an ICER of 24,123 €/QALY compared with the Dutch guideline strategy. The mutation strategy was subject to extended dominance by the CMS strategy. Thus, in this analysis the CMS strategy was the preferred choice.

Threshold analysis

Results of the threshold analysis in which we decreased the test costs for a CMS classification are shown in Supplementary Fig. S3. The NMB for the CMS strategy was lower compared with the mutation strategy when the test costs were between €500 and €200. From test costs from €100 or lower, the NMB of the CMS strategy was higher compared with the mutation strategy, indicating that the CMS strategy was the optimal strategy when the test costs were €100 or lower.

Scenario analysis

Results of the scenario analysis are reported in **Table 3**. The Dutch guidelines strategy served as the first comparison in the incremental cost-effectiveness analysis, given the lowest costs pp (€23,656). The mutation strategy without CMS4 resulted in an ICER of 32,633 €/QALY compared with the Dutch guidelines strategy, which is considered as cost-effective assuming a willingness-to-pay threshold of 50,000 €/QALY. Furthermore, the Dutch guideline strategy without CMS4 was subject to extended dominance and the mutation strategy was dominated by the mutation strategy without CMS4.

Probabilistic sensitivity analysis

The CEAC shows that the Dutch guideline strategy was most likely to give the highest NMB up to a willingness-to-pay threshold of 35,000 €/QALY (**Fig. 2**). From a willingness-to-pay of 35,000 €/QALY onwards, the mutation strategy had the highest probability to result in the highest NMB. The cost-effectiveness planes for the CMS strategy and mutation strategy compared with the Dutch guideline strategy are shown in Supplementary Fig. S4.

Expected value of (partial) perfect information

Figure 3 shows the population EVPI and EVPPI for a range of willingness-to-pay thresholds between €0 and €100,000 per QALY.

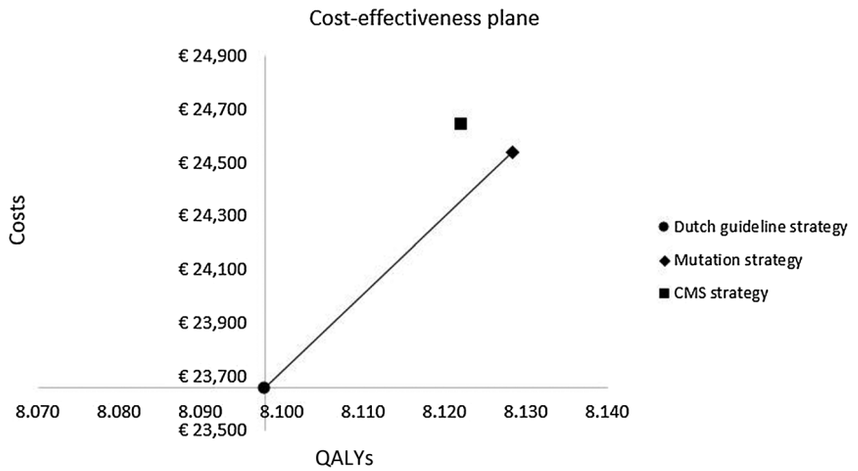

Figure 1.
Results of the base-case analysis presented in a cost-effectiveness plane. The cost-effectiveness plane depicts the discounted QALYs and discounted costs (€) of each strategy. The black line represents the cost-effectiveness frontier.

Table 3. Results of the scenario analysis in which we assumed resistance for adjuvant chemotherapy among patients with a CMS4 classification.

	Proportion of cohort treated	Colon cancer burden[a]		LY per individual (years)	QALYs per individual (years)	Costs per individual (€)	Net monetary benefit[b]	Incremental ICER (€/QALY)
		Recurrences	Deaths	Discounted	Discounted	Discounted		
Dutch guideline strategy	3.2%	162	137	9.832	8.097	23,656	381,200	*reference*
Dutch guideline strategy without CMS4[c]	2.4%	162	137	9.832	8.097	24,021	380,849	*dominated*[d]
Mutation strategy without CMS4[e]	9.2%	158	133	9.864	8.124	24,540	381,671	32,633
Mutation strategy	13.2%	158	133	9.864	8.123	24,563	381,571	*dominated*

Abbreviation: LY, life-years.
[a]Total during the lifetime of a cohort of 1,000 patients.
[b]On the basis of a willingness-to-pay threshold of €50,000/QALY.
[c]Patients with MSS AND pT4 receive chemotherapy, unless a patient is classified as CMS4.
[d]Through extended dominance.
[e]Patients with MSS status in combination with a mutation in BRAF and/or KRAS OR pT4 status receive chemotherapy, unless the patient is classified as CMS4.

Assuming a willingness-to-pay threshold of 50,000 €/QALY, the population EVPI was €19M, which is the expected value of eliminating all current decision uncertainty. Thus, this value represents the maximum value that decision makers should be willing to pay for future research to improve their decision-making on the use of CMS and gene mutation in stage II CC treatment selection. The prognostic parameters for MMR, BRAF, KRAS, and CMS status were the main drivers of the identified decision uncertainty as the population EVPPI for these parameters (€18M) was close to the population EVPI (€19M). We further evaluated the EVPPI for the CMS parameters and gene mutation (MMR, BRAF, and KRAS) parameters separately to examine whether the decision uncertainty was driven by one or both of these parameter subsets. Assuming a willingness-to-pay threshold of €50,000/QALY, we found a high EVPPI for both CMS parameters (€14M) and gene mutation parameters (€6M).

Discussion

In this early cost-effectiveness study, we compared the (cost-) effectiveness of three selection strategies to allocate chemotherapy in the stage II CC population: (i) the current Dutch guidelines, (ii) a selection strategy in which patients with a MSS status combined with a mutation in BRAF and/or KRAS or a MSS status combined with a pT4 received chemotherapy, and (iii) a selection strategy in which patients with CMS4 OR pT4 received chemotherapy. These strategies were completely focused on the prognostic value of the MMR, BRAF, KRAS, and CMS parameters. The CMS strategy and the mutation strategy were both more effective and more costly compared with the current Dutch guideline strategy. In an incremental cost-effectiveness analysis, the mutation strategy was the optimal strategy at a willingness-to-pay threshold of €50,000/QALY with an ICER of €28,893/QALY compared with the current Dutch guidelines. In addition, we evaluated the population EVPI and EVPPI for the MMR, BRAF, KRAS, and CMS parameters. Assuming a willingness-to-pay threshold of €50,000/QALY, the expected value of reducing decision uncertainty by conducting further research on the MMR, BRAF, KRAS, and CMS parameters was €18M.

Although the CMS strategy was dominated by the mutation strategy in the base-case analysis, the differences between both strategies were very small. To illustrate, comparing both the CMS strategy and mutation strategy to the current Dutch guideline strategy led to ICERs of €40,747/QALY and €28,893/QALY, respectively. Thus, assuming a willingness-to-pay threshold of €50,000/QALY, both strategies would be considered cost-effective compared with the current Dutch guidelines. In addition, in the sensitivity analysis in which we increased the recurrence risk with 10% in the CMS4 group, the CMS strategy became the optimal strategy with an ICER of €24,123/QALY and the mutation strategy was no longer considered as cost-effective as this strategy was subject to extended dominance by the CMS strategy. The results of this sensitivity analysis show that the optimal treatment decision depends on the prognostic value of the MMR, BRAF, KRAS, and CMS parameters, which were the biggest drivers of decision uncertainty in our VOI analysis. Given the weak underlying evidence, small differences in predicted QALYs and costs, and the high identified decision uncertainty, the optimal strategy cannot be determined on the basis of the currently available evidence.

When interpreting our results, it should be noted that the dataset available from the study of Guinney and colleagues, which was used for parametrization of the prognostic value of CMS, also included rectal cancer patients (approximately 15%). As the distribution of patients with colon cancer and rectal cancer is almost equal across the CMS

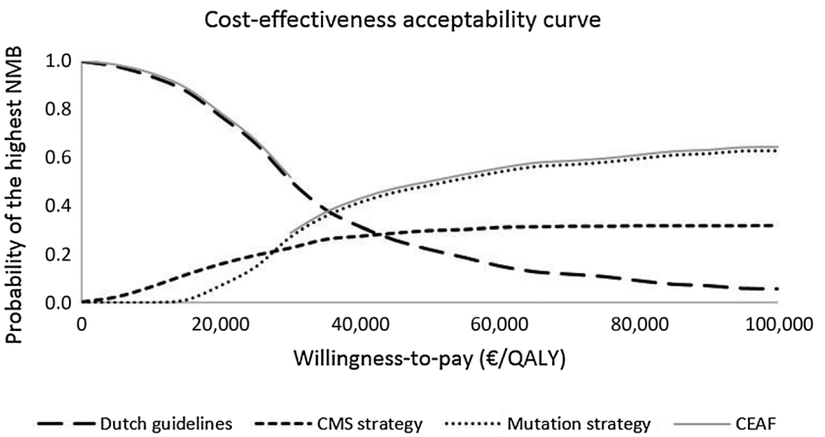

Figure 2.
CEAC for the three evaluated strategies. The plot represents the percentage of probabilistic analysis iterations for which a strategy is the optimal strategy relative to the other two strategies for a willingness-to-pay range of €0-€100,000 per QALY. The cost-effectiveness acceptability frontier (CEAF) depicts this same probability for the strategy that is optimal based on expected QALYs and costs for a willingness-to-pay range of €0-€100,000 per QALY.

subtypes and the proportion of rectal cancer patients was low, we expect that this had only a minor influence on the estimated HRs (7). Furthermore, it should be noted that in this study the molecular-based strategies were compared with the current Dutch guideline, which recommends adjuvant chemotherapy in patients with a MSS or pT4tumor. The Dutch guideline deviates from other international guidelines such as the European Society for Medical Oncology (ESMO) and American Society for Clinical Oncology (ASCO), as these include, besides MSS and pT4, also other high-risk features, that is, <12 lymphnodes evaluated, primary tumor perforation, poor tumor differentiation, extramural vascular invasion (ASCO only), and obstructive tumors (ASCO only) in the decision to select patients for adjuvant chemotherapy (42, 43). We were not able to compare the molecular-based strategies to strategies based on the ESMO and ASCO guideline recommendations as the high-risk features included in ESMO and ASCO guidelines were not included in the PATTERN model. As the ESMO and ASCO guidelines include more clinical and pathological high-risk factors than the Dutch guidelines, the percentage of treated patients would have been higher in a potential ESMO or ASCO strategy compared with the Dutch guideline strategy. If these clinical and pathologic factors partly correlate with the molecular markers, the added value of the molecular markers might be more limited for the ESMO and ASCO guideline.

In addition, it should be kept in mind that we assumed in the base-case analysis an equal treatment effect of adjuvant chemotherapy in all subgroups in the PATTERN model. That is, patients were selected for adjuvant chemotherapy solely based on their expected prognosis. To our knowledge, there are currently no indications for heterogeneous treatment effects in the clinical, pathologic, and biomarker subgroups. However, there are cautious indications that CMS4 patients are less likely to benefit from adjuvant chemotherapy (36–38, 44). We did not take into account this potential resistance in the base-case analysis. The rationale for this choice is that currently available evidence is weak. However, it is of great importance that more data will be collected in the near future on the predictive value of CMS. When sufficient data is available, model analyses should be updated. Alternatively, we conducted a scenario analysis in which we assumed that adjuvant chemotherapy has no effect in patients with CMS4. The results of this scenario analysis showed that it would be beneficial to exclude patients with CMS4 from adjuvant chemotherapy in case of resistance, because it leads to higher QALYs (less toxicity from ineffective treatment) and lower costs. This emphasizes the importance of including the predictive value of molecular markers in the decision making process, in addition to the prognostic value of these markers.

Conducting additional research which focuses on the MMR, BRAF, KRAS, and CMS parameters has the potential to improve decision-making on the optimal use of CMS and gene mutation data in stage II colon cancer treatment selection and to reduce current decision uncertainty. A suitable design for additional data collection is a prospective observational cohort study. More specifically, data could

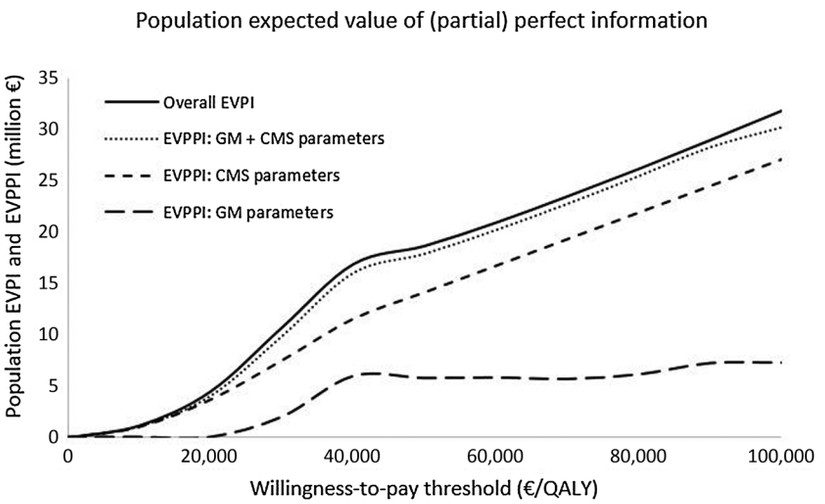

Figure 3.
Population EVPI and EVPPI for (a selection of) the parameters in the PATTERN model. The population EVPI reflects the expected value of eliminating uncertainty from all model parameters over a range of willingness-to-pay thresholds of €0 to €100,000/QALY. The population EVPPI reflects the expected value of eliminating uncertainty in the selected sets of prognostic parameters concerning the gene mutations (MMR, BRAF, and KRAS) and CMS, which are used to allocate adjuvant chemotherapy. The population EVPPI was depicted for the three following sets of parameters: (i) the MMR, BRAF, and KRAS parameters; (ii) the CMS parameters; and (iii) the MMR, BRAF, KRAS, and CMS parameters. Abbreviation: GM, gene mutation.

be obtained as part of PLCRC, an observational nationwide cohort study in the Netherlands (31). Given that the expected costs of an observational study are substantially lower than the EVPPI estimate identified in our study (€18M; ref. 45), further research would be valuable to reduce the current decision uncertainty and improve decision-making on the value of MMR, BRAF, KRAS, and CMS for treatment selection (46).

Before the CMS classification system could be used in daily clinical practice to guide adjuvant treatment decisions in the stage II colon cancer population, a number of challenges should be overcome. First, a more standardized procedure to determine a patients' CMS classification is needed. Nowadays, different procedures are used between studies, which may lead to heterogeneous results (7, 47). Thus, future research should focus on optimizing the CMS test procedure. Second, additional data collection is not only needed to reduce the uncertainty around the prognostic and potential predictive value of molecular markers, but also to gain more insight in the interconnectivity between the CMS classification system and clinical and pathologic high-risk features, such as pT stage and number of evaluated lymphnodes. To illustrate, a recent cohort study of 30 patients with stage II CC with a CMS4 classification showed that the 5-year overall survival (OS) differs between low-risk patients (5-year OS: 41.7%) and high-risk patients (pT4 or < 10 lymphnodes evaluated; 5-year OS: 68.0%), which suggests that clinical an pathologic characteristics are related to tumor biology (48). The association between CMS and clinical and pathologic features should be further investigated in a larger sample size to optimize the identification of high-risk stage II patients.

In conclusion, this is the first study that evaluates the cost-effectiveness of a CMS-based selection strategy for adjuvant chemotherapy in the stage II colon cancer population. Both the CMS-based and mutation-based strategy were more effective and more costly compared with the current Dutch guideline. Given a threshold of €50,000/QALY, the preferred option would be to treat patients according to their BRAF and KRAS mutation status in addition to their MMR status and pT4. However, there was substantial decision uncertainty concerning the choice of optimal selection strategy, with the MMR, BRAF, KRAS, and CMS parameters as the main drivers of this decision uncertainty. Given this decision uncertainty, the choice for the optimal strategy cannot be based on the currently available evidence. Additional research on the prognostic and predictive value of the MMR, BRAF, KRAS, and CMS parameters has the potential to reduce this decision uncertainty and improve decision-making on the use of molecular markers to guide the treatment selection.

Authors' Disclosures

M.J.E. Greuter reports grants from ZonMw during the conduct of the study. M. Koopman reports other support from Nordic Farma, Merck-Serono, Pierre Fabre, and Servier, and grants from Bayer, Bristol Myers Squibb, Merck, Roche, and Servier outside the submitted work. L. Vermeulen reports personal fees from Genentech, and grants from Pierre Fabre, MSD, Bayer, and Servier outside the submitted work. G.R. Vink reports grants from Servier, Sirtex, BMS, Bayer, Merck, Pierre Fabre, and Personal Genome Diagnostics outside the submitted work. V.M.H. Coupé reports grants from ZonMw during the conduct of the study, as well as grants from KWF, ZonMw, Novartis, and GSK outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

G. Jongeneel: Conceptualization, formal analysis, methodology, writing–original draft. **M.J.E. Greuter:** Conceptualization, supervision, methodology, writing–review and editing. **N. Kunst:** Writing–review and editing. **F.N. van Erning:** Writing–review and editing. **M. Koopman:** Writing–review and editing. **J.P. Medema:** Data curation, writing–review and editing. **L. Vermeulen:** Data curation, writing–review and editing. **J.N.M. Ijzermans:** Writing–review and editing. **G.R. Vink:** Writing–review and editing. **C.J.A. Punt:** Writing–review and editing. **V.M.H. Coupé:** Conceptualization, supervision, funding acquisition, writing–review and editing.

Acknowledgments

Financial support for this study was provided by a grant from ZonMw (grant no.: 848015007). ZonMw had no role in designing the study, interpreting the data, writing the manuscript, and publishing the report. The authors thank the registration team of The Netherlands Comprehensive Cancer Organization (IKNL) for the collection of the data for the NCR.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 20, 2021; revised March 28, 2021; accepted June 9, 2021; published first June 23, 2021.

References

1. Integraal Kankercentrum Nederland. Cijfers over kanker. http://www.iknl.nl. Accessed 24 March 24, 2020.
2. Quasar Collaborative Group. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet North Am Ed 2007; 370:2020–9.
3. Osterman E, Glimelius B. Recurrence risk after up-to-date colon cancer staging, surgery, and pathology: analysis of the entire Swedish population. Dis Colon Rectum 2018;61:1016–25.
4. Adjuvante systemische therapie coloncarcinoom, Dutch guidelines colorectal cancer. http://www.oncoline.nl. Accessed March 24, 2020.
5. Dienstmann R, Salazar R, Tabernero J. Personalizing colon cancer adjuvant therapy: selecting optimal treatments for individual patients. J Clin Oncol 2015; 33:1787–96.
6. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer 2017;17:79–92.
7. Guinney J, Dienstmann R, Wang X, De Reyniès A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015; 21:1350.
8. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer 2017;17:268.
9. Jongeneel G, Greuter MJE, Van Erning FN, Koopman M, Vink GR, Punt C, et al. Model-based effectiveness and cost-effectiveness of risk-based selection strategies for adjuvant chemotherapy in Dutch stage II colon cancer patients, accepted by *Therapeutic Advances in Medical Oncology*. Therap Adv Gastroenterol 2021;14:1756284821995715.
10. Phipps AI, Limburg PJ, Baron JA, Burnett-Hartman AN, Weisenberger DJ, Laird PW, et al. Association between molecular subtypes of colorectal cancer and patient survival. Gastroenterology 2015;148:77–87.
11. Roepman P, Schlicker A, Tabernero J, Majewski I, Tian S, Moreno V, et al. Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition. Int J Cancer 2014; 134:552–62.
12. Jongeneel G, Greuter M, van Erning F, Koopman M, Medema JP, Kandimalla R, et al. Modeling Personalized Adjuvant TreaTment in EaRly stage coloN cancer (PATTERN). Eur J Health Econ 2020;21:1059–73.
13. van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol 2014;38:448–54.
14. Jongeneel G, Klausch T, van Erning FN, Vink GR, Koopman M, Punt CJ, et al. Estimating adjuvant treatment effects in Stage II colon cancer: comparing the synthesis of randomized clinical trial data to real-world data. Int J Cancer 2020; 146:2968–78.

15. van den Braak RRC, Sieuwerts AM, Kandimalla R, Lalmahomed ZS, Bril SI, van Galen A, et al. High mRNA expression of splice variant SYK short correlates with hepatic disease progression in chemonaive lymph node negative colon cancer patients. PLoS One 2017;12:e0185607.
16. Ozawa T, Matsuyama T, Toiyama Y, Takahashi N, Ishikawa T, Uetake H, et al. CCAT1 and CCAT2 long noncoding RNAs, located within the 8q. 24.21 'gene desert', serve as important prognostic biomarkers in colorectal cancer. Ann Oncol 2017;28:1882–8.
17. Jorissen RN, Gibbs P, Christie M, Prakash S, Lipton L, Desai J, et al. Metastasis-associated gene expression changes predict poor outcomes in patients with Dukes stage B and C colorectal cancer. Clin Cancer Res 2009;15: 7642–51.
18. Marisa L, de Reyniès A, Duval A, Selves J, Gaub MP, Vescovo L, et al. Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value. PLoS Med 2013;10:e1001453.
19. Felipe de Sousa EM, Colak S, Buikhuisen J, Koster J, Cameron K, de Jong JH, et al. Methylation of cancer-stem-cell-associated Wnt target genes predicts poor prognosis in colorectal cancer patients. Cell Stem Cell 2011;9:476–85.
20. Kemper K, Versloot M, Cameron K, Colak S, FdS eM, de Jong JH, et al. Mutations in the Ras–Raf axis underlie the prognostic value of CD133 in colorectal cancer. Clin Cancer Res 2012;18:3132–41.
21. Laibe S, Lagarde A, Ferrari A, Monges G, Birnbaum D, Olschwang S, et al. A seven-gene signature aggregates a subgroup of stage II colon cancers with stage III. OMICS 2012;16:560–5.
22. Nederlandse zorgautoriteit. www.medicijnkosten.nl. Accessed March 20, 2020.
23. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27: 3109–16.
24. Ayvaci MU, Shi J, Alagoz O, Lubner SJ. Cost-effectiveness of adjuvant FOLFOX and 5FU/LV chemotherapy for patients with stage II colon cancer. Med Decis Making 2013;33:521–32.
25. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
26. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie 2015.
27. Vleugels JL, Greuter MJ, Hazewinkel Y, Coupé VM, Dekker E. Implementation of an optical diagnosis strategy saves costs and does not impair clinical outcomes of a fecal immunochemical test-based colorectal cancer screening program. Endosc Int Open 2017;5:E1197–E207.
28. Nederlandse Zorgautoriteit, Tarieventabel dbc-zorgproducten en overige zorgproducten. https://puc.overheid.nl/nza/. Accessed March 24, 2020.
29. Tilson L, Sharp L, Usher C, Walsh C, Whyte S, O'Ceilleachair A, et al. Cost of care for colorectal cancer in Ireland: a health care payer perspective. Eur J Health Econ 2012;13:511–24.
30. Pasmans CT, Tops BB, Steegs EM, Coupe V, Grunberg K, de Jong EK, et al. Micro-costing diagnostics in oncology: from single-gene testing to whole genome sequencing. medRxiv 2019:19009969.
31. Burbach J, Kurk S, Coebergh van den Braak R, Dik V, May A, Meijer G, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol 2016;55:1273–80.
32. Oppe M, Devlin NJ, Szende A. EQ-5D value sets: inventory, comparative review and user guide. Springer; 2007.
33. Jongeneel G, Greuter MJE, van Erning FN, Twisk JWR, Koopman M, Punt CJA, et al. Longitudinal effects of adjuvant chemotherapy and related neuropathy on health utility in stage II and III colon cancer patients: a prospective cohort study. Int J Cancer 2021;148:2702–11.
34. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value Health 2016;19:343–52.
35. Vijgen S, vF H, Obradovic M. Ziektelast in de praktijk; De theorie en praktijk van het berekenen van ziektelast bij pakketbeoordelingen. Zorginstituut Nederland 2018.
36. Pogue-Geile KL, Andre T, Song N, Lipchik C, Wang Y, Kim RS, et al. Association of colon cancer (CC) molecular signatures with prognosis and oxaliplatin prediction-benefit in the MOSAIC Trial (Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer). Am Soc Clin Oncol; 2019.
37. Allen WL, Dunne PD, McDade S, Scanlon E, Loughrey M, Coleman HG, et al. Transcriptional subtyping and CD8 immunohistochemistry identifies patients with stage II and III colorectal cancer with poor prognosis who benefit from adjuvant chemotherapy. JCO Precis Oncol 2018;2018:PO.17.00241.
38. Li Y, Yao Q, Zhang L, Mo S, Cai S, Huang D, et al. Immunohistochemistry-based consensus molecular subtypes as a prognostic and predictive biomarker for adjuvant chemotherapy in patients with stage II colorectal cancer. Oncologist 2020;25:e1968–e79.
39. Rothery C, Strong M, Koffijberg HE, Basu A, Ghabri S, Knies S, et al. Value of information analytical methods: report 2 of the ISPOR Value of information analysis emerging good practices task force. Value Health 2020;23: 277–86.
40. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. Med Decis Making 1998;18:95–109.
41. Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. Med Decis Making 2014;34:311–26.
42. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi64–72.
43. Costas-Chavarri A, Nandakumar G, Temin S, Lopes G, Cervantes A, Correa CM, et al. Treatment of patients with early-stage colorectal cancer: asco resource-stratified guideline. J Glob Oncol 2019;5:1–19.
44. Song N, Pogue-Geile KL, Gavin PG, Yothers G, Kim SR, Johnson NL, et al. Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. JAMA Oncol 2016;2:1162–9.
45. Kunst NR, Alarid-Escudero F, Paltiel AD, Wang S-Y. A value of information analysis of research on the 21-gene assay for breast cancer management. Value Health 2019;22:1102–10.
46. Fenwick E, Steuten L, Knies S, Ghabri S, Basu A, Murray JF, et al. Value of information analysis for research decisions—an introduction: report 1 of the ISPOR value of information analysis emerging good practices task force. Value in Health 2020;23:139–50.
47. Trinh A, Trumpi K, Felipe De Sousa EM, Wang X, De Jong JH, Fessler E, et al. Practical and robust identification of molecular subtypes in colorectal cancer by immunohistochemistry. Clin Cancer Res 2017;23:387–98.
48. Coebergh van den Braak RRJ, Ten Hoorn S, Sieuwerts AM, Tuynman JB, Smid M, Wilting SM, et al. Interconnectivity between molecular subtypes and tumor stage in colorectal cancer. BMC Cancer 2020;20:850.
49. Central Bureau for Statistics Website. www.cbs.nl. Accessed March 24, 2020.
50. Lonardi S, Sobrero A, Rosati G, Di Bartolomeo M, Ronzoni M, Aprile G, et al. Phase III trial comparing 3–6 months of adjuvant FOLFOX4/XELOX in stage II–III colon cancer: safety and compliance in the TOSCA trial. Ann Oncol 2016;27: 2074–81.
51. Attard C, Maroun J, Alloul K, Grima D, Bernard L. Cost-effectiveness of oxaliplatin in the adjuvant treatment of colon cancer in Canada. Curr Oncol 2010;17:17–24.
52. van den Brink M, van den Hout WB, Stiggelbout AM, Klein Kranenbarg E, Marijnen CA, van de Velde CJ, et al. Cost-utility analysis of preoperative radiotherapy in patients with rectal cancer undergoing total mesorectal excision: a study of the Dutch Colorectal Cancer Group. J Clin Oncol 2004;22:244–53.
53. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999;94:1650–7.