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Model-based effectiveness and cost-effectiveness of risk-based selection strategies for adjuvant chemotherapy in Dutch stage II colon cancer patients

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Abstract

Background: We aimed to evaluate the cost-effectiveness of risk-based strategies to improve the selection of surgically treated stage II colon cancer (CC) patients for adjuvant chemotherapy.

Methods: Using the 'Personalized Adjuvant TreaTment in EaRly stage coloN cancer' (PATTERN) model, we evaluated five selection strategies: (1) no chemotherapy, (2) Dutch guideline recommendations assuming observed adherence, (3) Dutch guideline recommendations assuming perfect adherence, (4) biomarker mutation OR pT4 stage strategy in which patients with *MSS* status combined with a pT4 stage or a mutation in *BRAF* and/or *KRAS* receive chemotherapy assuming perfect adherence and (5) biomarker mutation AND pT4 stage strategy in which patients with *MSS* status combined with a pT4 stage tumor and a *BRAF* and/or *KRAS* mutation receive chemotherapy assuming perfect adherence. Outcomes were number of CC deaths per 1000 patients and total discounted costs and quality-adjusted life-years (QALYs) per patient (pp). Analyses were conducted from a societal perspective. The robustness of model predictions was assessed in sensitivity analyses.

Results: The reference strategy, that is, no adjuvant chemotherapy, resulted in 139 CC deaths in a cohort of 1000 patients, 8.077 QALYs pp and total costs of €22,032 pp. Strategies 2–5 were more effective (range 8.094–8.217 QALYs pp and range 118–136 CC deaths per 1000 patients) and more costly (range €22,404–€25,102 pp). Given a threshold of €50,000/QALY, the optimal use of resources would be to treat patients with either the full adherence strategy and biomarker mutation OR pT4 stage strategy.

Conclusion: Selection of stage II CC patients for chemotherapy can be improved by either including biomarker status in the selection strategy or by improving adherence to the Dutch guideline recommendations.

Keywords: adjuvant chemotherapy, biomarkers, colon cancer, cost-effectiveness, personalized medicine, stage II

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Background

After surgical resection, patients with stage II colon cancer have around 15% chance of developing recurrence of disease.[1,2] The chance of developing a recurrence may be reduced by treating stage II patients with adjuvant chemotherapy after initial surgery. Several trials indicated small, but absolute benefits of adjuvant chemotherapy in these patients for both disease-free survival (DFS) and overall survival (OS). For example, the QUASAR trial indicated an absolute improvement in OS of 3.6% [95% confidence interval (CI), 1.0–6.0%] for fluorouracil monotherapy compared with observation.[3] Our recent meta-analysis of nine randomized

clinical trials estimated a statistically non-significant treatment effect in terms of DFS of 0.77 (95% CI, 0.43; 1.10) for fluorouracil monotherapy compared with observation and 0.93 (95% CI, 0.72; 1.15) for FOLFOX compared with fluorouracil monotherapy.[4] It should be noted that most of the included trials in the meta-analysis were not powered to estimate treatment effectiveness in the stage II colon cancer population.

To prevent the harms of overtreatment, only stage II patients at high risk of recurrence should be treated with chemotherapy. To better understand which stage II colon cancer patients are likely to benefit from chemotherapy, several studies were performed that identified prognostic high-risk characteristics that can be used for decision-making in daily clinical practice. The American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) published guidelines describing these high-risk characteristics. Both guidelines agreed on the following clinical and pathological high-risk factors: pT4, poor differentiation, tumor perforation, lymphovascular invasion, perineural invasion, and number of lymph nodes evaluated ($<$13 in the ASCO guideline and $<$12 in the ESMO guideline).[5,6] In the Netherlands, patients with a pT4 status combined with a Microsatellite Stable (*MSS*) status are eligible for adjuvant chemotherapy in stage II colon cancer.[7]

In addition to the clinical and pathological high-risk features included in the international guidelines, interest in the prognostic value of biomarkers is currently increasing. Examples of relevant biomarkers in stage II colon cancer are Microsatellite Instability (*MSI*), *BRAF* and *KRAS* status. The scientific literature describes longer DFS and OS for stage II patients with a *MSI* status compared with patients with a *MSS* status.[8,9] Furthermore, various studies showed worse DFS for patients with a mutation in *BRAF* and/or *KRAS* compared with patients with double wild type.[10] To illustrate, Hutchins *et al.* found that patients with a *BRAF* mutation and a *MSS* status had a 1.42 (95% CI, 0.80–2.54) times higher risk of recurrence than patients without a *BRAF* mutation and *MSS* status. For patients with a *KRAS* mutation, the risk of recurrence was 1.32 (95% CI, 1.04–1.67) higher than for patients without a *KRAS* mutation.[11]

Although the literature is promising regarding the prognostic value of biomarkers in addition to or instead of clinical and pathological factors, the evidence to incorporate these in daily clinical decision-making is limited. Thus, there is a knowledge gap as to which stage II patients do benefit from adjuvant chemotherapy. The cost-effectiveness of different (molecular-based) strategies for selecting stage II colon cancer patients for adjuvant treatment has not been assessed so far. Therefore, we aimed to evaluate molecular-based selection strategies for adjuvant chemotherapy in stage II colon cancer patients in terms of effectiveness and cost-effectiveness. For these analyses, we used the Personalized Adjuvant TreaTment in EaRly stage coloN cancer (PATTERN) model.[12]

Methods

PATTERN model

The PATTERN model has been extensively described elsewhere.[12] A flowchart of the model is shown in Figure 1 and model parameters are shown in Appendix 1. In brief, the PATTERN model is a Markov cohort model with a lifelong time horizon and a 1-month cycle length. Five health states are included: diagnosis, recurrence, 90-day mortality, death of other causes, and death of colon cancer. Data from the Netherlands Cancer Registry (NCR) were used for model quantification.[13] The NCR database consisted of 2271 stage II colon cancer patients with an median age of 73 (interquartile range: 64–79), diagnosed between 2002 and 2008 (Appendix Table 1). It was assumed that transition probabilities from diagnosis to 90-day mortality were due to surgical complications. Other transitions in the model were parametrized using parametric survival models including relevant clinical and pathological covariates. The parametric survival models only included patients without adjuvant chemotherapy. Subsequently, biomarker status was included in the model based on three external cohorts.[14] In addition, we included a hazard ratio (HR) for treatment effect of 0.73 for fluoropyrimidine monotherapy combined with oxaliplatin and a HR of 0.78 for fluoropyrimidine monotherapy, both based on trial data.[4] The PATTERN model was internally validated. Furthermore, the model was externally validated and updated if necessary using the 2015 NCR data.[12]

In the PATTERN model, 216 subgroups are distinguished based on age (50–95 in nine 5-year categories), number of lymph nodes evaluated

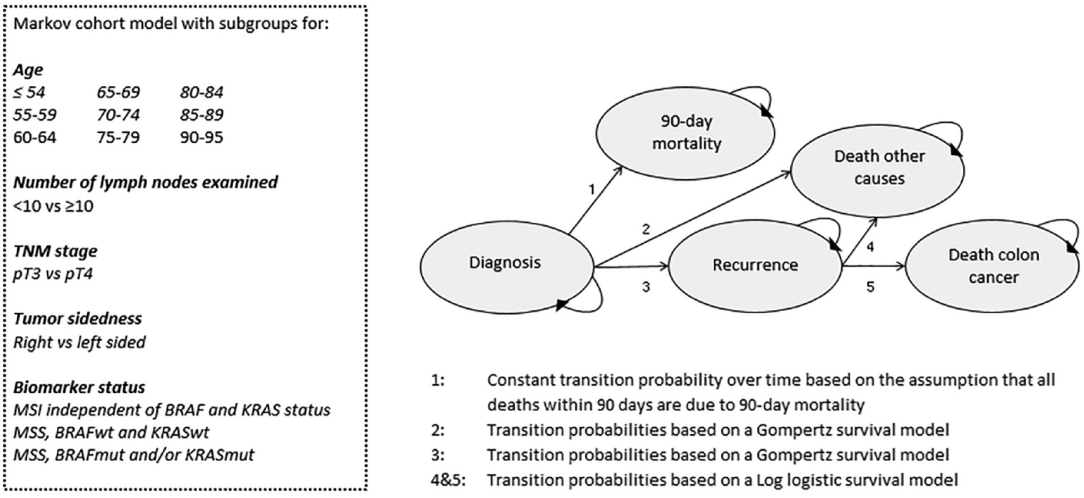

Figure 1. Flowchart of the personalized adjuvant TreaTment in EaRly stage coloN cancer (PATTERN) model.

(<10 and ⩾10, as registered in NCR), pT stage (pT3 and pT4), tumor site (left and right), and biomarker status (*MSI*, *MSS* without a mutation in *BRAF* and *KRAS* and *MSS* combined with a mutation in *BRAF* and/or *KRAS*). The subgroups in the PATTERN model can be used to evaluate different selection strategies for assigning adjuvant chemotherapy.

Strategies

Five selection strategies were evaluated:

(1) None of the patients receive adjuvant chemotherapy;
(2) Current adherence to the Dutch guidelines;
(3) Full adherence to the Dutch guidelines;
(4) *MSS* combined with a pT4 stage OR biomarker mutation (*BRAF* and/or *KRAS*) assuming full adherence;
(5) *MSS* combined with a pT4 stage AND biomarker mutation (*BRAF* and/or *KRAS*) assuming full adherence.

In the current adherence strategy (strategy 2), adjuvant chemotherapy administration was based on adherence to the Dutch guideline as observed in daily clinical practice, based on NCR data collected in 2015–2017. In the Dutch guideline, only patients with a pT4 *MSS* tumor are considered at high risk for recurrence of disease.[7] In the current adherence strategy, 21% of the high-risk patients and 3.5% of the low-risk patients are treated with adjuvant chemotherapy. In the full adherence strategy (strategy 3), adherence to the Dutch guideline was set at 100%. That is, all patients with a pT4 *MSS* tumor are treated with adjuvant chemotherapy, and no treatment is given to patients with other characteristics. In the biomarker mutation OR pT4 stage strategy (strategy 4), all patients with a *MSS* tumor combined with a pT4 stage OR a biomarker mutation (*BRAF* and/or *KRAS*) receive adjuvant chemotherapy, and no treatment otherwise. In the biomarker mutation AND pT4 stage strategy (strategy 5), only patients with an *MSS* tumor in combination with a mutation in *BRAF* and/or *KRAS* AND a pT4 stage receive adjuvant chemotherapy.

Costs

Table 1 shows an overview of costs and utilities. Costs were calculated from a societal perspective and included costs for initial surgery, the biomarker tissue test, medication, adverse events, absenteeism from work, patient's travel to the hospital, surveillance and recurrence of disease.[7,15–23] Costs of chemotherapy and adverse events were calculated separately for capecitabine monotherapy, CAPOX and FOLFOX. We assumed a treatment duration of 3 months for CAPOX, consisting of four cycles of 3 weeks.[7] For FOLFOX and capecitabine monotherapy we assumed a duration of 6 months.[24,25] The FOLFOX regimen consisted of 12 cycles of 2 weeks and the capecitabine monotherapy

Table 1. Overview of resource use, unit costs and utilities. All costs were standardized to 2018 Euros, using the consumer price index.[26]

	Value	Proportion	Reference
Resource use and costs			
Initial surgery	€12,987[a]		Nederlandse Zorgautoriteit[21]
Biomarker tissue test			Pasmans *et al*.[27]
MSI	€63		
BRAF/KRAS	€63		
Treatment cost per full regimen			
CAPOX	€5982		Adjuvante systemische therapie coloncarcinoom[7]; Nederlandse zorgautoriteit[15]; Hakkaart-van Roijen *et al*.[19]
% quitting before end of regimen		0.25[b]	André *et al*.[16]
FOLFOX	€10,284		Adjuvante systemische therapie coloncarcinoom[7]; Nederlandse zorgautoriteit[15]; Hakkaart-van Roijen *et al*.[19]
% quitting before end of regimen		0.25[b]	André *et al*.[16]
CAP	€989		Adjuvante systemische therapie coloncarcinoom[7]; Nederlandse zorgautoriteit[15]; Hakkaart-van Roijen *et al*.[19]
% quitting before end of regimen		0.13[b]	André *et al*.[16]
Adverse event cost per case			
Grade 3/4 neutropenia	€95		Nederlandse zorgautoriteit[15]; Ayvaci *et al*.[17]; André *et al*.[18]; Hakkaart-van Roijen *et al*.[19]
With oxaliplatin		0.411[d]	
Without oxaliplatin[c]		0.047[d]	
Febrile neutropenia	€3309		Nederlandse zorgautoriteit[15]; Ayvaci *et al*.[17]; André *et al*.[18]; Hakkaart-van Roijen *et al*.[19]
With oxaliplatin		0.018[d]	
Without oxaliplatin[c]		0.002[d]	
Grade 3/4 diarrhea	€50		Nederlandse zorgautoriteit[15]; Ayvaci *et al*.[17]; André *et al*.[18]; Hakkaart-van Roijen *et al*.[19]
With oxaliplatin		0.108[d]	
Without oxaliplatin[c]		0.066[d]	
Absenteeism costs per cycle[e]			Hakkaart-van Roijen *et al*.[19]
<55	€5296		
55–65	€4911		
Travel costs per cycle	€8		Hakkaart-van Roijen *et al*.[19]

(Continued)

Table 1. (Continued)

	Value	Proportion	Reference
Surveillance costs			
Colonoscopy	€850		Adjuvante systemische therapie coloncarcinoom[7]; Vleugels *et al.*[20]
Colonoscopy with complications	€1430	0.028	Vleugels *et al.*[20]
Ultrasound scan	€83		Adjuvante systemische therapie coloncarcinoom[7]; Hakkaart-van Roijen *et al.*[19]
CEA determination	€8		Adjuvante systemische therapie coloncarcinoom[7]; Nederlandse Zorgautoriteit[21]
Relapse costs	€41,868		Tilson *et al.*[22]
	Average value treated	**Average value untreated**	
Utilities			
Diagnosis month 1, before surgery	0.85	0.85	Burbach *et al.*[28]; Jongeneel *et al.*[29]
Diagnosis month 2–3, after surgery/before chemotherapy	0.81	0.85	Burbach *et al.*[28]; Jongeneel *et al.*[29]
Diagnosis month 4–6, during chemotherapy	0.83	0.86	Burbach *et al.*[28]; Jongeneel *et al.*[29]
Diagnosis month 7–18, 1 year after end chemotherapy	0.83	0.86	Burbach *et al.*[28]; Jongeneel *et al.*[29]
More than 1 year after chemotherapy	0.83	0.83	Burbach *et al.*[28]; Jongeneel *et al.*[29]
Recurrence month 1–60 after recurrence	0.45	0.45	Attard *et al.*[26]; Ness *et al.*[30]; van den Brink *et al.*[31]

[a]The DBC tariffs of 24 Dutch hospitals were averaged.
[b]We assumed that these patients dropped out halfway through the chemotherapy regimen. That is, for 25%/13% of the treated patients only the treatment costs of for the first half of the regimen were included in the evaluation.
[c]The values calculated for the treatment regimen without oxaliplatin were used for the sensitivity analysis in which part of the patients were treated without addition of oxaliplatin.
[d]Proportions apply across the entire 3-month treatment regimen.
[e]To calculate the absenteeism costs we assumed that; (1) the female to male ratio was 0.53/0.47,[12] (2) number of hours worked per week was 28 and 25 for women and 40 and 38 for men in the age groups <55 and 55–65, respectively,[32] and (3) patients do not work during chemotherapy.
CAP, capecitabine monotherapy; CAPOX, regimen that includes the drugs capecitabine and oxaliplatin; FOLFOX, regimen that includes the drugs leucovorin, fluoropyrimidine and oxaliplatin.

regimen consisted of eight cycles of 3 weeks. The adverse event rates were based on the MOSAIC trial.[18] For each adverse event category, the costs were calculated based on follow-up care. Follow-up care was defined as a visit to the outpatient clinic for neutropenia, a hospital stay of 5 days for febrile neutropenia and as oral rehydration medication for diarrhea.[15,19]

In the base-case analysis, we assumed that all patients that receive adjuvant chemotherapy were treated for 3 months with CAPOX in accordance with the Dutch guideline.[7] Surveillance was also based on the recommendations in the Dutch guideline and consisted of consultations every half-year during the first 3 years after surgery and yearly thereafter until 5 years after surgery.[7] Each

consultation is combined with a carcinoembryonic antigen (CEA) determination and an ultrasound scan of the liver (once a year). Furthermore, a colonoscopy is performed every 3 years starting 1 year after surgery.

Health-related quality of life

We estimated utilities using prospective data obtained within the Prospective Dutch ColoRectal Cancer cohort (PLCRC).[28] For the present study, 859 participants with an average age of 66 years and diagnosed with stage II or III colon cancer between 2011 and 2019 were selected (Appendix Table 3). Because there were no significant differences in health-related quality of life (HRQoL) between stage II and III patients, both stages were analyzed together. HRQoL was assessed with the EQ-5D-5L, which consists of five questions evaluating the health dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[33] The patients' scores on these health dimensions were transformed into a utility score using the Dutch tariff.[34]

To inform the model, average health utilities were calculated in six time periods separately for treated and untreated patients. The following time periods were defined: before surgery, after surgery and before start chemotherapy, during chemotherapy, first 12 months after chemotherapy and more than 12 months after chemotherapy. A full overview of estimated utilities, baseline characteristics of the PLCRC cohort per time period and more details on the estimations on the utilities are shown in Table 1 and Appendix 2.

Outcome

Model outcomes for each strategy included the number of recurrences and deaths due to colon cancer in the lifetime of 1000 patients, life-years, quality-adjusted life-years (QALYs), total lifetime costs per patient and the net monetary benefit (NMB). Costs and effects were discounted annually with 4% and 1.5%, respectively.[19] The NMB was calculated as (*total effect* × *threshold*) − *total cost*. In addition, we conducted an incremental cost-effectiveness analysis. First, strategies were ordered from lowest to highest costs. Incremental cost-effectiveness ratios (ICERs), which is the difference in costs divided by the difference in QALYs, were calculated between consecutive non-dominated strategies. A strategy was considered as dominated when there was an alternative strategy or combination of strategies that was more effective at equal or lower costs. In agreement with the recommendations of the National Healthcare Institute, a strategy was considered as cost-effective when the ICER does not exceed the threshold value of €50,000 per QALY.[35]

Sensitivity analyses

To assess the impact of uncertainty in our model parameters on the results of the cost-effectiveness analysis, eight one-way sensitivity analyses were conducted. First, we studied the impact of an imperfect adherence rate, that is, 50%, for the selection strategies 3 (Dutch guidelines), 4 (biomarker mutation OR pT4 stage), and 5 (biomarker mutation AND pT4 stage) as literature and NCR data showed that guidelines are not always followed in daily clinical practice.[13,36] In a second sensitivity analysis, we studied the impact of prescribing capecitabine monotherapy to 30% of the treated patients and CAPOX to 70% of the treated patients, as observed in the NCR dataset.[13] In this sensitivity analysis, treatment effect, drug costs and adverse event rates were adjusted. In a third sensitivity analysis, we studied the impact of a treatment with FOLFOX. The IDEA trials showed that a 3 month treatment regimen with FOLFOX is inferior to a 6 month treatment regimen with FOLFOX.[24,25] Therefore, patients were treated with 6 months of FOLFOX in this sensitivity analysis. The same treatment effect was assumed as for 3 months of CAPOX,[4] but drug costs and the period of disutility were adjusted. In the other sensitivity analyses, we decreased and increased the treatment effect by 10%, we decreased the drug costs by 10%, we decreased the health utility during treatment and the 12 months thereafter for patients who receive chemotherapy by 10%, we decreased the dropout rate to 0% and we repeated the analysis with international discounting rates (3% for costs and effects annually).[37]

Furthermore, a probabilistic sensitivity analysis (PSA) was performed using Monte Carlo simulation to investigate the joint impact of parameter uncertainty. The Monte Carlo simulations consisted of 1000 iterations for all evaluated strategies with a fixed set of parameters per iteration.

To graphically illustrate the uncertainty surrounding the deterministic outcomes, incremental costs and effects compared with the reference strategy were plotted on a cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve was constructed, depicting the proportion of PSA samples in which each of the simulated strategies is cost-effective, that is, with the highest NMB, as a function of the willingness-to-pay threshold. More detailed information of the PSA is provided in Appendix 3.

Finally, to assess the impact of varying the risk of recurrence in the biomarker subgroups on model predictions, two scenario analyses were conducted in which we changed the HRs to develop a recurrence in the biomarker subgroups, while maintaining the same overall risk of recurrence in the population. More detailed information on the scenario analyses is provided in Appendix 3.

Results

Effectiveness

The model predicted 165 recurrences and 139 colon cancer deaths when none of the patients receives chemotherapy (Table 2). All other strategies in which (part of the) patients were treated with chemotherapy (range treated patients 4.8%–43.2%), were more effective compared with no chemotherapy. The most effective strategy was the biomarker mutation OR pT4 stage strategy; compared with the reference strategy the number of recurrences and colon cancer deaths decreased with 14.8% and 15.0%, respectively. Predicted QALYs were lowest in the no adjuvant chemotherapy strategy with 8.077 QALYs per patient. All other evaluated strategies predicted higher QALYs in the range of 8.094–8.217 per patient.

Cost-effectiveness

The predicted costs per patient were lowest in the reference strategy in which no chemotherapy is given [€22,032 per patient (pp)]. The majority of the costs concern initial surgery and surveillance costs. The costs for the other strategies were higher in a range of €22,404–€25,102 pp (Table 2). The cost difference compared with the reference strategy was mainly caused by the increasing proportion of patients treated with adjuvant chemotherapy, leading to increased treatment costs. The biomarker mutation OR pT4 strategy had the highest NMB at a willingness-to-pay threshold of 50,000 €/QALY (€385,754), suggesting that this strategy is the preferred strategy at this threshold.

In the incremental cost-effectiveness analysis, the no adjuvant treatment strategy served as the first comparator, because this strategy led to the lowest discounted costs and QALYs (Table 2). The next best strategy was the full adherence strategy, which had higher total average costs (€22,697 pp) and effects (8.136 QALYs pp), leading to an ICER of €11,181/QALY. The current adherence strategy was dominated by the biomarker mutation AND pT4 stage strategy, given the lower effects and higher costs. The biomarker mutation AND pT4 stage strategy was subject to extended dominance by the full adherence strategy, which means that the costs and benefits of this strategy are inferior to a combination of the strategies based on no adjuvant treatment and full adherence. The strategy based on biomarker mutation OR pT4 stage was more effective and more costly compared with full adherence, which led to an ICERs of €29,767/QALY. Thus, given the Dutch threshold of €50,000/QALY, optimal use of resources would be to treat patients with either the full adherence strategy and biomarker mutation OR pT4 stage strategy. A visual representation of the cost-effectiveness frontier is shown in Figure 2.

Sensitivity analysis. Results of the one-way sensitivity analyses are shown in Appendix Table 4. For the sensitivity analyses in which we varied adherence rate, treatment effect, drug costs, discount rates, health utility, dropout rate and the percentage of patients that were treated with CAPOX, we found similar results as in the base-case analysis. That is, ICERS were similar for all evaluated strategies.

Deviating ICERs were found in the sensitivity analysis in which we treated patients with FOLFOX for 6 months, although the ordering of the strategies remained the same. The biomarker mutation OR pT4 stage strategy was no longer considered as cost-effective (ICER: 76,038 €/QALY). This deviating result was caused by the higher costs for 6 months of FOLFOX compared with 3 months of CAPOX on the one hand and the lower QALYs due to the longer treatment duration on the other hand.

Figures 2 and 3 present the results of the PSA. For all evaluated strategies, all points on

Table 2. Results of the cost-effectiveness analysis. Strategies are ordered according to increasing discounted costs.

	Proportion of cohort treated (%)	Colon cancer burden[a]		LY per individual (years)		QALYs per individual (years)		Costs per individual (€)		NMB[b]	Incremental ICER (€/QALY)
		Recurrences	Deaths	Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted		
No adjuvant chemotherapy	0.0	164.8	139.3	11.148	9.808	9.183	8.077	23,277	22,032	381,809	reference
Biomarker mutation AND pT4	4.8	160.1	135.1	11.188	9.842	9.217	8.107	23,642	22,404	382,936	dominated[c]
Dutch guideline - current adherence	5.3	161.7	136.7	11.172	9.829	9.203	8.094	23,700	22,462	382,257	dominated
Dutch guideline - full adherence	11.0	155.1	130.8	11.228	9.877	9.252	8.136	23,923	22,697	384,119	11,181
Biomarker mutation OR pT4	43.2	140.4	118.3	11.346	9.978	9.347	8.217	26,283	25,102	385,754	29,767

[a]During the lifetime of a cohort of 1000 individuals.
[b]Calculated at a willingness-to-pay threshold of 50,000 €/QALY.
[c]Through extended dominance.
LY, life-years; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life-years.

the cost-effectiveness plane are located in the north-east quadrant, where strategies are more effective but also more costly compared with no adjuvant chemotherapy. The cost-effectiveness acceptability curve shows that up to a willingness-to-pay threshold of 11,000 €/QALY, the proportion of PSA samples in which the no adjuvant chemotherapy strategy has the highest NMB is larger than for any other strategy (Figure 3). Subsequently, the full adherence strategy dominates up to a willingness-to-pay threshold of 29,000 €/QALY. From a willingness-to-pay of 29,000 €/QALY onwards, the biomarker mutation OR pT4 strategy has the highest NMB in the largest proportion of PSA samples compared with all other strategies. The results of the PSA were also used to determine the 95% credibility intervals around the base-case results, which are shown in Appendix Table 5.

Results for the scenario analyses, in which we varied the HRs determining the risk of recurrence in the biomarker subgroups, are shown in Table 3. In both scenarios, results were comparable to the base-case results.

Discussion

This study evaluated the effectiveness and cost-effectiveness of risk-based strategies to improve the selection of stage II colon cancer patients for adjuvant chemotherapy. We evaluated the following five strategies: (1) no adjuvant chemotherapy, (2) Dutch guideline recommendations assuming observed adherence, (3) Dutch guideline recommendations assuming perfect adherence, (4) a biomarker mutation OR pT4 strategy in which patients with *MSS* status combined with a pT4 stage or a *BRAF* and/or *KRAS* mutation receive treatment and (5) a biomarker mutation AND pT4 stage strategy in which patients with *MSS* status combined with a *BRAF* and/or *KRAS* mutation and a pT4 stage receive adjuvant treatment. The no adjuvant chemotherapy strategy was considered as the reference strategy. All strategies were more effective than no adjuvant chemotherapy in terms of QALYs pp (range 8.094–8.217) and colon cancer deaths per 1000 patients (range 118.30–140.38), but also more costly (range €22,404–25,102 pp). Considering a threshold value of €50,000/QALY, optimal use of resources would be to treat patients with either the full adherence strategy and biomarker mutation OR pT4 stage strategy.

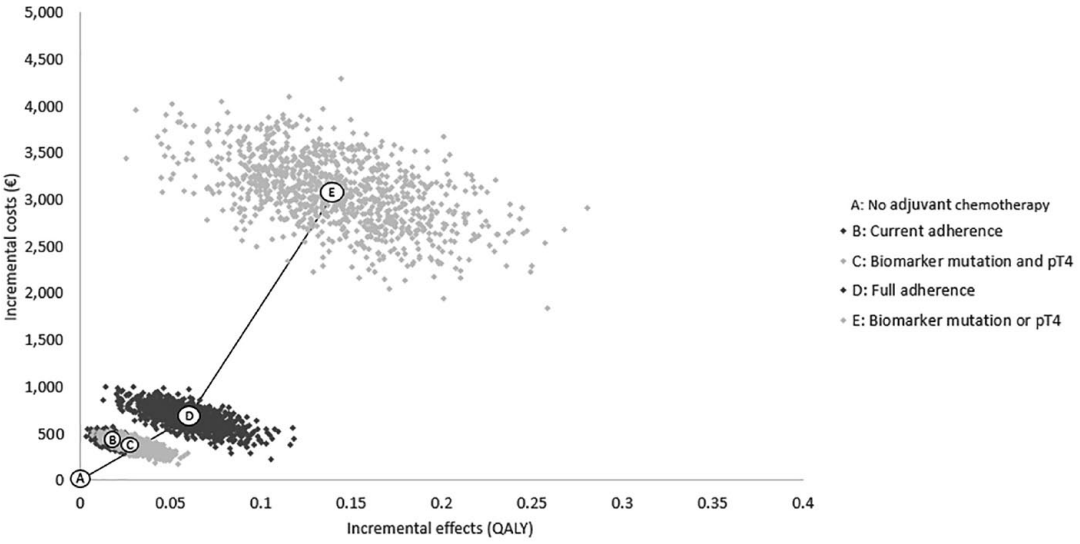

Figure 2. Incremental cost-effectiveness plane depicting the incremental discounted costs (€) and incremental discounted quality-adjusted life-years (QALYs) of each strategy compared with the reference strategy in which none of the patients receives adjuvant chemotherapy. The black line represents the cost-effectiveness frontier, which connects successive points on a cost-effectiveness plane. Note that strategy B and C are not on the cost-effectiveness frontier. The circles with letters A–E refer to the deterministic estimates per strategy.

To our knowledge, the PATTERN model is the first decision model that can evaluate the effectiveness and cost-effectiveness of different (molecular-based) selection strategies for adjuvant chemotherapy in stage II colon cancer patients. An earlier model-based study by Avayci *et al.*[17] showed that fluoropyrimidine in combination with oxaliplatin was not cost-effective compared with no adjuvant chemotherapy in stage II colon cancer. However, the evaluation of Avayci *et al.* did not distinguish between different patient groups, and was therefore not able to evaluate different selection strategies for adjuvant chemotherapy.

Assigning chemotherapy in a personalized manner is a hotly debated topic in oncology. Molecular-based selection strategies for adjuvant chemotherapy are already evaluated for other types of cancer, but not for early stage colon cancer. To illustrate, the results of Roth *et al.*[38] and Jahn *et al.*[39] suggest that assigning adjuvant chemotherapy based on molecular features may be a cost-effective alternative to standard guideline recommendations for early stage lung cancer and early stage breast cancer, respectively. It should be noted that these studies evaluated molecular-based selection strategies using a multiple-gene assay including 14 or 21 genes, while in the current study only *MSS*, *BRAF* and *KRAS* status were considered for treatment allocation in the biomarker strategies. Nevertheless, our results are in line with the findings of these studies since the biomarker mutation OR pT4 stage strategy was found to be cost-effective.

Based on pooled trial data, we included a HR for treatment effect of 0.73 for fluoropyrimidine combined with oxaliplatin.[4] Although the sample size was large in this pooled analysis, results were not statistically significant. To investigate the uncertainty around treatment effect we conducted a one-way sensitivity analysis, in which we decreased and increased treatment effect by 10%. This analysis showed that changes in treatment effect had no influence on the model outcomes.

When interpreting the results of our model predictions, it should be noted that we did not take potential predictive treatment effects into account. That is, we used the same treatment effect in all subgroups when treating patients with the same treatment regimen. A previous study demonstrated a predictive effect for stage II and III colon cancer patients with a microsatellite

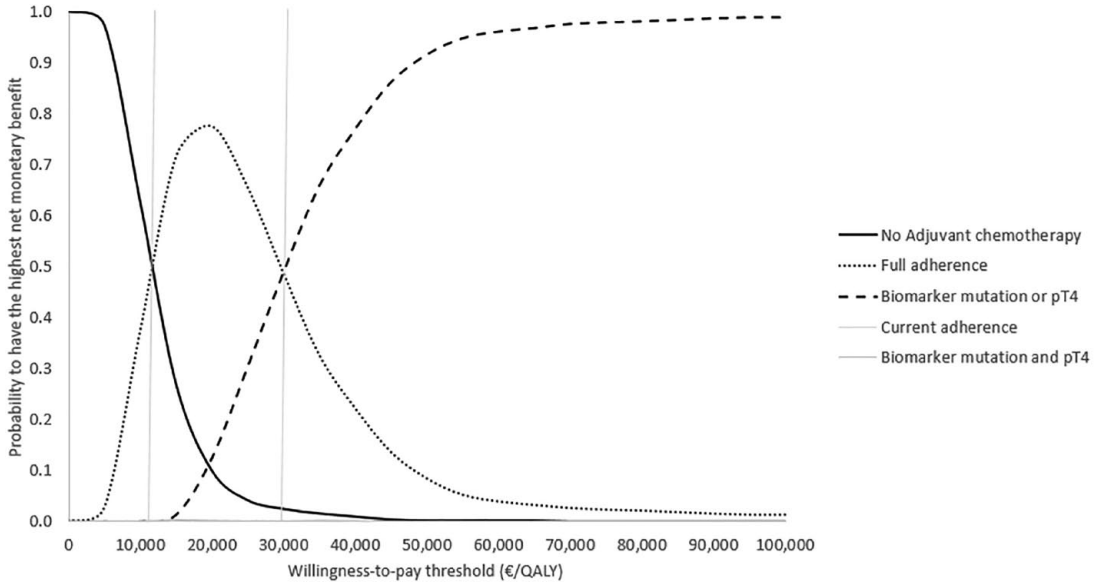

Figure 3. Cost-effectiveness acceptability curve of all evaluated strategies. The plot represents the percentage of PSA iterations for which a strategy is the most cost-effective strategy relative to all other strategies for a willingness-to-pay range of €0–€100,000 per quality-adjusted life-year (QALY). Note that this percentage is zero for the current adherence strategy and biomarker mutation AND pT4 stage strategy, as these strategies never result in the highest net monetary benefit in a willingness-to-pay range of €0–€100,000 per QALY.

instable (*MSI*) tumor. This study showed that these patients have a resistance to fluoropyrimidine monotherapy.[40] It should be noted that in our model-based evaluation, none of the *MSI* patients were selected for adjuvant chemotherapy in both the base-case analysis and the sensitivity analyses. For the *BRAF* and *KRAS* biomarkers, no predictive treatment effect has yet been found in stage II colon cancer patients. Thus, cost-effectiveness of the biomarker mutation OR pT4 stage strategy in the base-case analysis was solely based on the poorer prognosis of patients with a mutation in *BRAF* and/or *KRAS*. Model predictions need to be updated as soon as sufficient evidence for any differences in treatment effect in the biomarker subgroups becomes available.

The health utilities used as input for the current study were derived from patient-level data from the PLCRC cohort. It should be noted that the difference in health utility between patients with and without adjuvant chemotherapy during chemotherapy and the first 12 months thereafter was at 0.03 relatively small, indicating that adjuvant chemotherapy has only a small impact on quality of life. As a result, the strategy in which the highest percentage of the cohort is treated is likely to lead to the highest number of QALYs. To evaluate the impact of a higher burden of adjuvant chemotherapy on model predictions, we performed a sensitivity analysis in which we increased the difference in health utility between patients with and without adjuvant chemotherapy from 0.03 to 0.08. Although the ICERs for the full adherence strategy and the mutation OR pT4 strategy increased in this sensitivity analysis, these strategies remained the optimal use of resources assuming a threshold value of €50,000/QALY. In addition, these strategies resulted in the highest QALYs compared with the other evaluated strategies.

In line with the Dutch guideline recommendations,[7] treatment consisted of CAPOX in the base-case analysis. Literature and data show that not all patients are treated with oxaliplatin-based chemotherapy in clinical practice, which is primarily due to the clinical condition of the patients.[36] Therefore, we conducted a sensitivity analysis in which 70% of the patients were treated with CAPOX and 30% with capecitabine monotherapy based on the NCR dataset used for model quantification. This analysis showed similar results compared with the base-case analysis. In

Table 3. Results of scenario analyses in which we varied the ratios for risk of recurrence between the biomarker subgroups.

	Proportion of cohort treated (%)	Colon cancer burden[a]		LY per individual (years)	QALYs per individual (years)	Costs per individual (€)	NMB[b]	Incremental ICER (€/QALY)
		Recurrences	Deaths	Discounted	Discounted	Discounted		
Scenario 1; 10% decrease in risk to develop a recurrence in the *MSI* and *MSS*dwt biomarker subgroup								
No adjuvant	0.0	163.4	138.2	9.816	8.084	21,987	382,222	Reference
Biomarker mutation AND pT4 stage	4.8	158.7	134.0	9.851	8.115	22,357	383,384	Dominated[c]
Dutch guideline – current adherence	5.3	160.5	135.6	9.837	8.101	22,419	382,652	Dominated
Dutch guideline – full adherence	11.0	154.0	129.9	9.883	8.142	22,660	384,460	11,561
Biomarker mutation OR pT4 stage	43.2	138.3	116.6	9.991	8.229	25,032	386,427	27,333
Scenario 2; 10% increase in risk to develop a recurrence in the *MSI* and *MSS*dwt biomarker subgroup								
No adjuvant	0.0	166.5	140.7	9.797	8.067	22,090	381,262	Reference
Biomarker mutation AND pT4 stage	4.8	161.8	136.6	9.831	8.096	22,466	382,348	Dominated[c]
Dutch guideline - current adherence	5.3	163.4	138.0	9.819	8.085	22,518	381,726	Dominated
Dutch guideline - full adherence	11.0	156.6	132.0	9.867	8.128	22,749	383,626	10,910
Biomarker mutation OR pT4 stage	43.2	142.8	120.3	9.962	8.202	25,187	384,930	32,576

[a]Total during the lifetime in a cohort of 1000 patients.
[b]Calculated at a willingness-to-pay threshold of 50,000 €/QALY.
[c]Through extended dominance.
ICER, incremental cost-effectiveness ratio; LY, life-years; NMB, net monetary benefit; QALYs, quality-adjusted life-years.

addition, from NCR data we know that a small proportion of the patients switch from CAPOX to fluoropyrimidine monotherapy during the regimen. We were not able to evaluate the impact of any treatment modifications as there are no estimates for the effectiveness of such combined treatment regimens. Moreover, since the difference in treatment effectiveness between both regimens is relatively small (0.73 *versus* 0.78), the impact of treatment modifications on model predictions will be limited.

In addition, it should be noted that in the Netherlands, the recommended treatment duration for stage II colon cancer patients is recently revised from 6 months to 3 months for CAPOX. However, FOLFOX is a regularly prescribed regimen in other European countries, for which the recommended duration is still 6 months. Therefore, we conducted a sensitivity analysis in which patients were treated with FOLFOX for 6 months. The biomarker mutation OR pT4 stage strategy was no longer considered as cost-effective in this sensitivity analysis with an ICER of €76,038/QALY, due to the higher costs and lower QALYs. Our results indicate that including biomarkers in the decision-making process is not beneficial in a setting where 6 months of FOLFOX is the most prescribed treatment.

Furthermore, the guidelines for selection of stage II colon cancer patients for adjuvant chemotherapy are not strictly followed in daily clinical practice.[36] Dutch national registry data show adherence rates of 21% for high-risk patients and 3.5% for low-risk patients as simulated in

the current adherence strategy. The current adherence strategy was dominated by extended dominance in the incremental base-case analysis by the full adherence strategy, which resulted in an ICER of €11,181/QALY. However, even a 50% adherence to the Dutch guidelines is already cost-effective (ICER €12,195/QALY) as shown in our one-way sensitivity analysis.

In the current study we had biomarker data available for only a limited number of patients, which resulted in broad confidence intervals. As a result, we did not vary the biomarker parameters in the PSA. As an alternative, we conducted two scenario analyses in which we varied the HRs to develop a recurrence in the biomarker subgroups, while the overall risk of recurrence in the population was kept identical. The results of these two scenario analyses were in line with the base-case results. However, the uncertainty surrounding the HRs for developing a recurrence dependent on biomarker status could be considered a limitation of the study and an area where additional data would be useful to improve model-based predictions.

In conclusion, this is the first model-based study that evaluated risk-based selection strategies for adjuvant chemotherapy in stage II colon cancer. All of the evaluated strategies in which (part of the) patients were treated with adjuvant chemotherapy were more effective and more costly compared with no adjuvant chemotherapy. Given a threshold of €50,000/QALY, optimal use of resources would be to treat patients with either the full adherence strategy and biomarker mutation OR pT4 stage strategy. These findings indicate that selection of stage II colon patients for chemotherapy can be improved by either including biomarker status in the selection strategy or improving adherence to current Dutch guideline recommendations.

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Data availability
The decision model is available upon reasonable request from the Decision Modeling Center, which is part of the Amsterdam University Medical Center, location VUmc. The registry data used for model development are upon request available from the Netherlands Cancer Registry.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Ethical approval
Ethical approval was not required for this study. This modeling study did not include any human participants or animals.

All data of the Netherlands Cancer Registry are anonymized and de-identified. According to the Central Committee on Research involving Human Subjects (CCMO, The Hague, Netherlands), this study type does not require ethics approval in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

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Supplemental material
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