Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach

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Declarations

All authors contributed to the work, are aware of, and agree to the submission. Any other person or body with an interest in the manuscript, such as our funders and employers, are also aware and agreed on the submission.

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Ethics approval and consent to participate

The observational study from 1993 to 2010, including 2049 patients diagnosed with CRC at Oslo University Hospital, was approved by the Regional Ethics Committee (Norway) for Medical Research (REK approval 1.2005.1629).

The study with data collected from the National Patient Register (NPR) was approved by the Regional Ethics Committee (Norway). The reference number is S-02113 (2013/83).

Availability of data and material

The Markov model and the data used are presented in a separate article (1).

For modelling the Markov model, we used Excel 2016, and for the PSA we used @risk 7.5 for Excel from Palisade.

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Abstract

New and emerging advances in colorectal cancer (CRC) treatment combined with limited health care resources highlight the need for detailed decision-analytic models to evaluate costs, survival and quality adjusted life-years. The objectives of this article were to estimate the expected lifetime treatment cost of CRC for an average 70-year-old patient and to test the applicability and flexibility of a model in predicting survival and costs of changing treatment scenarios.

The analyses were based on a validated semi-Markov model using data from a Norwegian observational study (2049 CRC-patients) to estimate transition probabilities and the proportion resected. In addition, inputs from the Norwegian Patient Registry, guidelines, literature, and expert opinions were used to estimate resource use.

We found that the expected lifetime treatment cost for a 70-year-old CRC patient was €47,300 (CRC stage I €26,630, II €38,130, III €56,800, and IV €69,890). Altered use of palliative chemotherapy would increase the costs by up to 29%. A 5 percentage point reduction in recurrence rate for stages I–III would reduce the costs by 5.3% and increase overall survival by 8.2 months. Given the Norwegian willingness to pay threshold per QALY gained, society's willingness to pay for interventions that could result in such a reduction was on average €28,540 per CRC patient. The life years gained by CRC treatment were 6.05 years.

The overall CRC treatment costs appear to be low compared to the health gain, and the use of palliative chemotherapy can have a major impact on cost. The model was found to be flexible and applicable for estimating the cost and survival of several CRC treatment scenarios.

Keywords: Colorectal cancer, Markov model, cost, surgery, chemotherapy, analyse innovations.

1. Introduction

Cancer is a major cause of morbidity and mortality in the Western world, with colorectal cancer (CRC) being the second most common cancer in women and the third most common cancer in men [1]. Norway is among the countries in the world with the highest incidence of CRC [2]. As the number of CRC cases increases with an ageing population, and new costly drugs are launched in the market, we expect a substantial increase in the cost of CRC treatment. For healthcare providers making decisions regarding reimbursement, it is important to consider the cost-effectiveness of preventive and treatment alternatives in order to optimise resource allocation.

Decision-analytic models are useful to achieve optimal allocation of resources because these models can (i) provide information about the burden of diseases, (ii) within a certain disease identify treatment strategies with potential health gains, and (iii) evaluate the cost-effectiveness of new treatment options (Table 1). Regarding (i), decision-analytic models can be used in comparative cost-of-illness studies, which compare the cost of CRC treatment with the cost of treating other diseases [3]. Regarding (ii), for new ideas and innovations in surgery, chemotherapy, screening, and primary prevention, a decision-analytic model is useful for exploring the potential incremental cost and incremental health gain (reduced mortality, recurrence rate, and health related quality of life). Based on these estimates and the willingness to pay (WTP) threshold (the value for an incremental health gain), we can identify the maximum acceptable amount to invest in these interventions. Furthermore, results from such explorative analyses can be used to evaluate budget impacts for the healthcare sector [4]. Regarding (iii), decision-analytic models are useful when estimating the cost-effectiveness of single or combined interventions both within and between intervention strategies such as surgery, chemotherapy, and screening.

Table 1

The first objective of this study was to estimate the expected lifetime cost and survival of CRC treatment for an average 70-year-old CRC patient based on a general, validated decision-analytic model [5]. The second objective was to explore the applicability and flexibility of the model by performing several analyses of changing CRC treatment strategies, the consequences of increasing the number of patients

receiving palliative chemotherapy (including antibodies), the consequences of decreasing the recurrence rate, and the effect of diagnosing CRC at an earlier stage (by screening or other measures). With these two objectives, we explored the general properties of the CRC decision-analytic model and how it contributed at all three levels as shown in Table 1.

2. Methods

We applied the perspective of the healthcare sector and included costs of diagnostic and staging investigations, surgery (major resection and palliative surgery without resection), treatment for complications, preoperative (neoadjuvant) and postoperative (adjuvant) treatment, follow up, curative treatment of recurrence, palliative treatment of recurrence and primarily non-resectable disease, and visits to general practitioners. We measured the health outcomes in both life years (LYs) and quality-adjusted life years (QALYs).

2.1 The model

In brief, the costs and survival in this paper were estimated based on a semi-Markov model, details of which were published in [5]. The flow of CRC patients was simulated in the model from CRC diagnosis at the age of 70 years through periods of treatment and healthy periods until the patients were 100 years of age or had died from CRC or other causes (Figure 1). Each arrow reflected the probability of an average CRC patient moving from one health state to another during one cycle or maintaining in the same health state (follow the loops). The patient *entered* the model at the time of primary diagnosis in one of the TNM stages (I, II, III or IV), and the first step included the costs of primary work-up and treatment during the first year after diagnosis. The following year, any patient who received curative treatment moved to the health state "disease free", which means that the tumour had been resected and that there was no evidence of macro- or microscopic residual tumour (R0-resection) - locoregionally and no radiological evidence of distant metastases. Alternatively, the patient was not curable at the time of diagnosis (non-resectable

disease) and moved to the palliative health state or experienced recurrence after an apparently curative resection or died of CRC or other causes. From 'disease free', the patients could die of other causes or move to one of the three recurrence states. The majority of patients entering one of the three recurrence states (local and/or distant recurrence) received palliative chemotherapy. Some patients underwent resection with curative intent, often combined with (neo)adjuvant (radio)chemotherapy, and some received only best supportive care. The probabilities of receiving the treatments depended on the type of recurrence.

Fig. 1

For the majority of the patients in stage IV, the intent of treatment was palliation. Patients not eligible for any specific anti-cancer therapy, due to old age or poor general health, received supportive care until entering 'Dead by CRC'. Palliative treatment mainly consisted of chemotherapy and/or targeted therapy (antibodies), but a small proportion was also offered radiotherapy. The treatment algorithm for 1st, 2nd, and 3rd lines of palliative chemotherapy is illustrated in Figure 2, which is a sub-model of the model in Figure 1. The treatment depended on age and health status (fragile), and there were several treatment options in each treatment line. When the disease progressed during the initial palliative drug treatment (1st line), a new treatment was usually offered (2nd line), and when the patient experienced additional progression a 3rd line of treatment could be offered [6, 7]. FLIRI is a combination of Irinotecan and 5-fluorouracil/folinic acid (5-FU/FA), the latter of which was based on a Nordic protocol (Nordic FLv). FLOX is a therapeutic combination of Oxaliplatin and 5-FU/FA. The figures at each arrow in Figure 2 indicate the conditional probability, and the figures in brackets express the joint (total) probability of receiving a certain type of treatment [5]. For each treatment in the decision tree, separate cost models were developed that included the costs of medication, CT scanning, complications, and treatment by nurses, pharmacists, and medical practitioners. The model was adjusted for non-compliance and discontinuation of chemotherapy, and this decision tree (Figure 2) was the basis for estimating the average cost of palliative treatment.

Fig. 2

In the model, the duration of one cycle was set to one year, and for each health state, there was a cost model estimating the cost of the health service provided per person per year. We estimated the total CRC cost and the survival of an average CRC patient diagnosed at the age of 70 years. Survival and QALYs were half-cycle corrected. For costs, standard half-cycle corrections were not modelled but were modelled indirectly using empirical data to estimate CRC treatment cost considering compliance and mortality. Time dependency in the calculation of probabilities of recurrence and death was captured in the model by including tunnel states.

2.2 Data and data sources

We used Norwegian population-based data when possible. Transition probabilities were based on an observational study including 2049 patients diagnosed with CRC from 1993 to 2010 at Oslo University Hospital (referred to as OUS data) [8, 9]. The sample was population-based, and their ages correspond to CRC patients in general. The OUS data were also used to identify those treated with resection during primary treatment. Information from the Norwegian Patient Registry (referred to as NPR data) from 2003 and 2004, previously used in Aas et al. [10], was used to quantify hospital treatments, except primary surgical treatment, including hospital stays for complications and metastatic surgical treatment. The cost estimates from the NPR were average numbers and not adjusted for age. Radiotherapy and chemotherapy (both adjuvant and palliative) were based on treatment guidelines and expert opinions. Other data sources were national life tables, internationally published papers, and expert opinions (three co-authors – one surgeon, one oncologist, and one gastroenterologist). For complementary information about the assumptions and data used for the analyses not presented in the paper, see Online Resource 1.

We used the individual-level OUS data to estimate rates of recurrence, disease-free survival, and overall survival. We controlled for age and gender in the estimations, and for the model we predicted the rates for a 70-year-old CRC patient [5].

The cost inputs for the treatments provided during the first year are presented in Online Resource 1, and the cost input of palliative chemotherapy is shown in Table 9 in Appendix 1 of Joranger et al.[5].

The probability of receiving an R0-resection after recurrence and all the conditional probabilities on the right side of squares A and Q in Figure 2 were based on expert opinion [5]. To estimate QALYs, we assumed that the health-related quality of life (HRQoL) for patients with CRC and those without CRC was 0.74 and 0.80, respectively [11, 12].

We applied a 4% discount rate for costs, overall survival, and QALYs. In addition, we ran a separate analysis with zero discounting for overall survival [13, 14]. All cost were estimated in euros (€1 = NOK 7.79) and adjusted to 2016 euros using the consumer price index (2.62% for the period 2011–2016).

The Norwegian guidelines for economic evaluation of health interventions [13] recommend using NOK 500,000 per life year in full health (1 QALY) for analyses across sectors. Adjusted for inflation (2.34% yearly) [15], the Norwegian WTP threshold per QALY gained was then calculated to be €82,800 in 2016 euros.

This value was also used as a proxy for the WTP for a life-year gained.

2.3 Estimation of costs and cost-effectiveness

The estimation of the total treatment cost (output) was mainly based on the CRC stage at the time of diagnosis, the recurrence rate for each stage, the type of recurrence, the probability of re-recurrence, the probability of receiving palliative chemotherapy, the probability of receiving certain kinds of palliative chemotherapy, the distribution between colon and rectal cancer in the population at different stages, the compliance when following up and completing chemotherapy, and the survival time.

For the analysis on changing treatment regarding chemotherapy and screening, we estimated the incremental cost, and for analysing the effect of reduced recurrence rate and the cost-effectiveness of

overall CRC treatment, we used the incremental cost-effectiveness ratio (ICER), which is defined by the differences in costs relative to differences in health outcomes.

The total cost of CRC treatment and the cost-effectiveness of overall CRC treatment was estimated by comparing the treatment for an average 70-year-old CRC patient (defined as the "base case") to a population without CRC. For all the analyses of changes in treatment, the changes were compared with the base case.

2.4 Validation and uncertainty analysis

The model has been validated by [5] for face, internal, cross, and external validity. The external validation for relative survival was based on data from The Cancer Registry of Norway. The validation concluded that a satisfactory match was found with other models and real-life observations for both costs and survival time without any preceding calibration of the model. Because the model was partly based on data from 1993–2010, the validation was also done against observations and models based on data from the same time period.

We used one-way and multi-way sensitivity analyses to explore parameter-, methodological-, and model-structure uncertainty. To explore the total uncertainty concerning the use of expert opinion, we used probabilistic sensitivity analysis (PSA). In the PSA, we gave beta distributions to all the parameters based on expert opinions and assumed that the upper level of the 95% confidence interval was +30% of the expected value and that the lower was −30%. To explore the uncertainty in the estimation of survival for untreated patients in Section 3.3, both deterministic analysis and PSAs were used.

3. Results

3.1 Base case cost and survival

3.1.1 Costs according to disease stage

From a healthcare perspective, the total expected lifetime CRC costs and loss of life years (LYs) were reported for an average 70-year-old CRC patient according to the disease stage at the time of diagnosis (Table 2). Based on our model, a 70-year-old CRC patient had an expected lifetime CRC cost of €47,300. The expected costs increased with TNM stage as follows: stage I, €26,630; stage II, €38,130; stage III, €56,800; and stage IV, €69,890.

Table 2

3.1.2 Type and phase of treatment

The treatments with the greatest impact on total lifetime costs (Table 2) were surgery of the primary tumour (€20,390) and palliative chemotherapy (€10,920). Costs related to diagnostic examinations, adjuvant treatment, and follow-up in general were modest for all stages. For stage IV, the main costs were "surgery – major resection" (primary tumour) (€19,230), "surgery - other" (€21,660), and "palliative chemotherapy" (€25,260). The palliative chemotherapy cost estimates were for the average patient that started with some kind of palliative chemotherapy treatment, and their treatment is shown in Figure 2. "Surgery – major resection" was the major cost component for stages I and II. Variations between stages depended on differences in treatment, the mix of colon and rectum cases, and the proportion of patients experiencing cancer recurrence.

When we categorised treatment costs according to clinical pathway, starting with primary examinations and ending with palliative chemotherapy (Table 2), expected lifetime costs varied according to TNM stage at the time of diagnosis. Patients in stage IV had the highest expected costs both for primary treatment

(€42,050) and palliative treatment (€25,260), while patients in stage III had the highest expected costs of treatment for recurrence (€6360).

The expected treatment cost of only the chemotherapy for the group of CRC patients receiving some kind of palliative chemotherapy was on average €40,850 per patient. This was estimated by multiplying the probability (in parentheses) of receiving the various treatment options shown in Figure 2 with the costs of the respective chemotherapy regimens given in Table 1 in Online Resource 2. These estimates were then summarized to provide the expected total costs for these various treatments. Of this, epidermal growth factor receptor inhibitors (EGFR-inh) such as cetuximab/panitumumab and the related 3rd line treatment with irinotecan in Figure 2 jointly constituted 36.0% of the costs (equal to the sum of the 3rd line scenarios in Table 2 in Online Resource 2), and bevacizumab and the related treatment FLIRI/FLOX jointly (both branch C, D and F, G in Figure 2) constituted 34% of the costs (equal to the sum of 27.5%, 3%, 3%, 0.3% in Table 2 in Online Resource 2). Table 3 in Online Resource 2 shows the total treatment cost per patient when receiving all of the chemotherapy treatments in one separate scenario/branch defined in Figure 2. Costs were estimated for seven different branches, where the most expensive branches (C, D, and E in Figure 2) cost €97,000 euro. Of the total cost of palliative CRC chemotherapy, this branch generated 40.7% of the cost when we adjusted for which treatment the patients actually received and the proportion of patients who did not undergo all treatments (equal to the sum of the first row in Table 2 in Online Resource 2).

3.1.3 Recurrence and palliative chemotherapy

Variations in treatment costs for a patient could also be estimated according to certain *low- and high-cost treatment pathways*. In the *low-cost treatment pathway* (stage I patients), we included the following cost components: (i) diagnostics, (ii) resections without complications, and (iii) five-year follow-up. In the *high-cost estimate* (patients with recurrence), we included (i) diagnostics (ii) treatment costs in the first year, (iii) one-year follow-up, (iv) one-year treatment for recurrence in the second year after being diagnosed with CRC, (v) one-year follow-up after recurrence for those who achieved R0, and (vi) palliative chemotherapy at the end of the second year, at the end of the third year, and at the end of the fourth year. The

combination of palliative chemotherapy included in the *high-cost treatment pathway* was bevacizumab + FLIRI in the 1st line, FLOX in the 2nd line, and EGFR-inh + irinotecan in the 3rd line.

The expected costs for a *low-cost-treatment pathway* (stage I without recurrence) were estimated to be €16,450, and the expected costs for a *high-cost-treatment pathway* (with recurrence) were €125,830 and €142,540 for patients in stages I and IV, respectively (Table 2).

3.1.4 Survival, QALYs, and years lost

According to the model, the life expectancy for a CRC patient diagnosed at the age of 70 years was 9.3 years (7.0 years with discounting), implying a loss of 6.3 years (4.1 years discounted) compared to an average 70-year-old Norwegian (Table 2). The loss of discounted QALYs was 3.7 on average and 1.4, 2.6, 3.8, and 7.9 for stage I, II, III, and IV, respectively. Based on the model, we found that life expectancy was 14.0 years (1.6 years lost) for a patient in stage I and 1.5 years (14.1 years lost) for a patient in stage IV.

3.1.5 Uncertainty

According to the deterministic sensitivity analysis, for most input parameters the model was insensitive to a 20% change. The expected total costs were most sensitive to changes in frequency of surgery and the use of bevacizumab in palliative treatment (see Online Resource 3).

We performed a PSA to simultaneously account for all uncertainty caused by parameters based on expert opinion and found that the 95% credible interval (CrI) for the total costs was ±3% of the mean, and for the effect on life expectancy the 95% CrI was ±0.5% of the mean (see Online Resource 3).

3.2 Changing treatment strategies

3.2.1 Scenarios of palliative chemotherapy

When health authorities estimate the costs of introducing new and costly drugs, such as EGFR-inh or bevacizumab, they may assume that 100% of the CRC patients will receive the treatment. Our analyses

considered that these drugs were only relevant to subgroups of CRC patients [16, 17]. We assumed that 61% of all 70-year-old patients diagnosed at stage IV, or experiencing recurrence after R0 resection, would receive palliative chemotherapy [17]. The different treatment paths and related probabilities are shown in Figure 2, and costs per treatment are shown in Table 1 in Online Resource 2. To account for higher compliance, we estimated the cost per patient (undiscounted) when fully treated according to the defined palliative chemotherapy scenarios compared to no palliative treatment (see Figure 2 and Online Resource 2). The cost difference between the full treatment scenario "*5-FU/FA (1st line) and EGFR-inh + irinotecan (2nd line)*" (Q, R in Figure 2) (€52,030) and the scenario "*bevacizumab and FLIRI (1st line), FLOX (2nd line), and EGFR-inh + irinotecan (3rd line)*" (C, D, E) (€97,000), which represents the strategy with bevacizumab, was €44,970 (see Table 3 in Online Resource 2). Furthermore, we found that using "*bevacizumab and FLIRI*" (C) rather than only "*FLIRI*" (J) in the 1st line would have an extra cost of €33,030 (see Table 3 in Online Resource 2).

Alternative chemotherapy schedules (protocols) – impact on costs

To show the importance of uncertainty in the input data and the possible impact of future decisions, we estimated the effect of changes in both prices and probabilities (see Table 1 in Online Resource 4). The use of bevacizumab varies between different countries. In the model, we assumed that 29% of patients receiving palliative chemotherapy were treated with this drug. We estimated the cost difference from the base case for the following new scenarios (treatment changes 1–4 in Table 3):

1. All patients who receive palliative chemotherapy are treated with bevacizumab (all patients move through box B in Figure 2).
2. No patients receive bevacizumab (all patients going through box B in the base case move instead through I in Figure 2).
3. Patients receiving combination chemotherapy (FLIRI/FLOX) as the 1st line of treatment in the base case instead receive bevacizumab and FLIRI/FLOX (all patients who move through I in the base case move instead through B).
4. The price of bevacizumab is reduced by 50%.

The treatment alternatives most sensitive to changes in treatment costs were the "*EGFR-inh (cetuximab/panitumumab) +irinotecan treatment*" and "*bevacizumab + FLIRI treatment*" (see Table 3). If we e.g. assume alternative 1 in Table 3 (*All patients getting palliative chemotherapy receive bevacizumab*), the expected total costs for a CRC patient would increase by 14%. This change in treatment strategy would thus increase the treatment costs in Norway by €27.8 million per year (assuming 4268 diagnosed CRC patients per year) and by €5.3 per capita per year. If bevacizumab was not offered (*FLOX and FLIRI was used without bevacizumab,* alternative 2), the expected total costs would decrease by 5% compared to the current strategy, and the Norwegian health sector's expenditure would decrease by €10.9 million (€2.1 per capita). If those receiving "*FLIRI/FLOX*" as a 1st line of treatment were instead to receive "*bevacizumab + FLIRI/FLOX*" (alternative 3), then the costs would increase by 8% per patient and increase the health sector's expenditure in Norway by €16.3 million (€3.1 per capita).

Table 3

Increased use of chemotherapy in the elderly

CRC is common in elderly patients, and approximately 40% of CRC patients are 75 years of age or older. What then would be the effect on CRC costs of treating a greater number of elderly patients with palliative chemotherapy? One extreme scenario would be to assume that all patients would receive palliative chemotherapy. We estimated the change from the base case by analysing the following scenarios (treatment change 5-8 in Table 3):

5. All patients who are not disease free after treatment receive palliative chemotherapy (more patients move into the sub-model illustrated by Figure 2).
6. Given we are in scenario 5 above, all patients in this scenario receive bevacizumab as a 1st line of treatment (all patients receiving palliative chemotherapy move through box B in Figure 2).
7. Ten percentage points compared to base case move from 5FU/FA-treatment (often elderly patients) to combination chemotherapy with bevacizumab (10 percentage points move from box P to B).

8. Ten per cent more CRC patients receive palliative chemotherapy among those diagnosed with stage IV or recurrence.

One extreme scenario above is number 5 – all patients who are not disease free after treatment would receive palliative chemotherapy regardless of age and general health. Based on the current pattern of chemotherapy prescription, the costs for an average CRC patient would increase by 9% (Table 3). If all patients received "*bevacizumab as a 1st line of treatment*" (scenario 6), the expected total costs would increase by 29%, and the health sector's expenditure would increase by €58.2 million (€11.1 per capita).

3.2.2 Reduced recurrence rate

Recurrence of cancer implies more treatment and greater loss of life expectancy. We assumed a 5 percentage point reduction in the 10-year recurrence rate from 32.5% (base case) to 27.5% for stages I–III. To achieve this, we used the same percentage reduction in the transition probabilities moving patients from the state of 'disease free' to the state of recurrence for all years and for all three stages. All other inputs were as in the base case. Reduced recurrence rate reduced the treatment costs because of fewer surgeries and other treatments for recurrence, less palliative treatment, and a reduced number of patients for follow up after recurrence. However, reduced recurrence also caused more patients to complete the follow up after the primary treatment. Furthermore, reduced recurrence caused increased survival.

According to the model, the 5 percentage point reduction described above would reduce the costs by €2190 per patient (5.3%) and increase the overall survival by 0.68 years (0.43 years discounted). Out of the 4268 persons diagnosed with CRC in 2015, 80% were diagnosed with stage I, II, or III disease (OUS data). Hence, a reduction in the recurrence rate would imply 2310 LYs saved per year in Norway (0.68 years * 4268 CRC patients * 0.80) and reduce health care costs by €7.47 million per year (€1.44 per capita).

Given the Norwegian WTP threshold per QALY gained, society's willingness to pay for interventions that could contribute to a 5 percentage point reduction in recurrence was €28,540 per CRC patient when survival was discounted by 4% per year (€2190 + [0.43 year * 0.74 QALYs per LY * €82,800 per QALY)

in stage I, II, or III (€43,850 with undiscounted survival). In total, this account for €97 million per year (€28,540 per patient * 4268 patients per year * 0.80 in stage I, II, or II) and €18.8 per capita.

Table 4

3.2.3 Primary prevention

Prevention of CRC might be achieved by screening and removing precursor lesions, increased physical activity, modifications to diet and lifestyle (including smoking cessation and prevention of excessive body weight), and use of anti-inflammatory drugs. Preventive measures might reduce the number of cases in all CRC stages, and the outcome of preventive intervention for CRC can be estimated using the model. In our analysis, we assumed that prevention affects all stages with the same percentage reduction in the number of people who develop CRC. Thus, we used the cost estimates of the four CRC stages as an estimate of the cost reduction of saving one person from developing CRC and used the estimation of loss of life years for the same stage to estimate the number of years saved.

The reduction in costs caused by preventing one CRC case was estimated to be €47,300; see Tables 2 and 4. In addition, according to the model, each CRC case prevented gained 6.3 years (4.1 years discounted). Given the WTP threshold value, society's willingness to pay for preventive interventions was estimated to be €353,660 per CRC case prevented (€47,300 + [3.7 QALY * €82,800 per year]) when survival was discounted by 4%.

3.2.4 Screening – gain from stage migration

To assess the effect of stage migration on healthcare costs, we used CRC screening as an example. Randomised controlled trials have been carried out for CRC screening in several countries, and our model

estimates were based on results from the UK and Denmark [18, 19]. In both trials, faecal occult blood tests were used to detect cancer at an early, asymptomatic stage in order to improve survival and reduce the CRC treatment costs. Table 2 in Online Resource 4 shows that CRC patients diagnosed through a screening programme have a more favourable stage distribution than those in the control groups. This is a potential gain from screening, provided that the early-stage, screen-detected tumours do not represent overdiagnosis, e.g., tumours that would never have emerged as clinical tumours within the lifespan of the person. The stage migration effect was greater in the UK trial than in the Danish trial. Patients in the screening groups were 50–74 years old and 45–74 years old, respectively, in these trials.

Applying data from Denmark [19], the reductions in costs were €14.9 per screened individual and €7300 per CRC detected (both excluding the cost of screening). The corresponding results based on the UK trial [18] were €21.6 and €10,306, respectively. The changes in cost caused by screening were a result of stage migration from more advanced cancer when diagnosed due to symptoms (base case) to a less advanced and even pre-cancerous stage when detected pre-symptomatically at screening. In the model, stage migration reduced both the cost of primary treatment and the number of recurrences. When fewer patients were diagnosed with cancer at stages III and IV and did not experience recurrence, the number of patients receiving palliative treatment decreased. In cases where screening results in excessive overdiagnosis of early and non-cancerous lesions, the consequences for costs will be more complex.

3.3 Productivity in CRC treatment

To estimate the productivity of CRC treatment in general, we need to quantify the survival gained by CRC treatment. Therefore, we used the estimated life expectancy according to CRC stages (Table 2), compared this value to the life expectancy for a cohort of hypothetical patients *without any CRC treatment,* and estimated the gain to society per euro used for CRC treatment. Online Resource 5 presents the analysis of survival without CRC treatment as well as the model and the assumptions used.

We have not found any relevant survival data for a patient without treatment. Instead, we used a separate Markov model to estimate the survival for the group (see Online Resource 5). In this model, we followed the patients from the age of 70 years to 100 years or until death, and we assumed the following transition

probabilities from one stage to another: stage I to stage II 0.583 (CI used in the PSA: 0.3–0.9) per year, stage II to stage III 0.656 (0.3–0.9), and stage III to stage IV 0.747 (0.31–0.85). The assumptions were based on the literature, where the transition probabilities were estimated using calibrations[20-22]. For patients in stage IV, we assumed the total annual probability of CRC death and non-CRC death to be 0.582.

The gain in LYs from the overall CRC treatment was estimated to be 6.05 years. For all stages, and given the Norwegian WTP threshold per QALY, the gain was €5.2 per euro used for CRC treatment (€7.8 if survival was not discounted). For stages I, II, and III, the gain per euro used for CRC treatment was €12.7, €8.1, and €5.0, respectively.

These estimates depended partly on the estimated life expectancy for a cohort of hypothetical non-treated CRC patients, estimated separately with a Markov model. The parameter uncertainty for the transition parameters between CRC stages used in this separate model was considerable. Thus, we performed a PSA for this separate Markov model, and based on the upper level of expected survival time for untreated patients we estimated the gain for society to be €5.5 per euro used for CRC treatment and €3.6 when using the lower level (€5.7 if survival was not discounted).

4. Discussion

4.1 The results of the analyses

The estimated lifetime healthcare cost for an average 70-year-old CRC patient was €47,300 and varied with disease stage at diagnosis from €26,630 to €69,890. Compared with the empirical ("model-free") Norwegian study by Aas [10], our overall cost estimate was 39% higher, but only 1.3% higher after adjusting for differences in the included costs and time horizon (see more in [5]). The increase in costs according to the disease stage was similar to increases reported by Ladabaum et al. [23] and Frazier et al.

[21], while Brown et al. [24] found an increase in costs for stages I–III, but a decrease for stages IV. However, comparing our CRC cost with those in non-Norwegian studies is difficult because of differences in unit costs and assumptions for the analyses [25]. Nevertheless, we compared our results with those of a recent Irish study by Tilton et al. that described the treatment regime and other important conditions in such detail that it allowed for adjustment based on relevant differences [26]. When adjusting for the exchange rate, the annual Irish inflation between 2008 and 2011, and important differences in unit prices and treatment regimens between the two studies, the cost difference between Tilton's model and our model was −3.0%, −1.3%, 3.6%, and −1.2% for stages I, II, III, and IV, respectively, all within the estimated credible intervals of the former study (see more in [5]).

The cost for CRC treatment estimated by the model appeared modest compared to the number of QALYs gained by the same treatment. For all stages and given the Norwegian WTP threshold per QALY gained, the gain to society was €5.2 per euro allocated for CRC treatment and €12.7, €8.1, and €5.0 for stages I, II, and III, respectively, per euro allocated for CRC treatment. These estimates depended heavily on the estimated survival time for non-treated patients (Online Resource 5, Fig. 2). However, the gain would still be €3.6 per euro spent on treatment for all stages despite using the lower level of the estimated CrI. The public health service in Norway is often criticised for high costs, but our results indicate that the surplus to society seems to be considerable for CRC treatment.

A 20% change in the cost of the various palliative chemotherapies, including, for example, drug costs and time-use costs, had a minor effect on the total CRC costs (<2%), while expanded use of palliative chemotherapy could increase the total costs up to 29% (€11.3 per capita). Two factors are especially important for a possible increase in cost – the use of bevacizumab or EGFR-inh and an increased use of palliative chemotherapy in elderly patients. The current trend to use EGFR-inh more frequently as a 1st line of treatment and the increased use of palliative chemotherapy in the elderly can therefore have a profound impact on cost [16, 27, 28]. Because many evaluations have time horizons of 10–30 years, PSA based on parameter probability distributions estimated from "yesterday's data" can be misleading. Therefore, CRC evaluations with long time horizons need to not only focus on high-quality palliative

chemotherapy data, but also make reasonable assumptions about changes in future palliative treatments and perform sensitivity analyses based on these assumptions and alternative scenarios.

We found that a 5 percentage point reduction in the 10-year recurrence rate for stages I–III would reduce CRC costs by €2190 per patient and increase overall survival by 0.68 years per patient. Based on these findings and the declared acceptable WTP threshold value of €82,800 per QALY gained, the Norwegian health sector should be willing to pay €97 million in total per year to achieve this reduction in recurrence rate (see Section 3.7). Approximately 3000 colorectal resections for malignancy are performed each year in Norway. Assuming that each colorectal surgeon should perform at least 15 resections each year to maintain their competence, a maximum of 200 surgeons is needed in this field [29]. A comprehensive training programme (initial colorectal surgery training and yearly follow-up training) could use modern educational tools (such as simulators, operations on animals, etc.) along with workshops and lectures by highly experienced and skilled colorectal surgeons, radiologists, and pathologists. Assuming that such a comprehensive training programme would cost €300,000 per surgeon and that the effect would be a reduction in recurrence rate by 5 percentage points, the investment would be paid back after only 11 CRC operations per surgeon.

The estimates for a 5 percentage point reduction in the 10-year recurrence rate are also relevant when estimating possible gains from post-cancer prevention such as lifestyle interventions (diet, physical activity, etc.). Some studies show significant effects of such interventions [30-38], but these effects are highly uncertain because of the scarcity of high-quality randomised controlled trials [37, 38]. When evaluating strategies for post-CRC cancer prevention, we also have to consider the possible effects on HRQoL, physical functioning, tolerance to interventions, morbidity, and non-CRC mortality [37, 38].

For the screening analysis, the estimates did not consider that some patients diagnosed with CRC in the screening group would have died of something else before their CRC had produced symptoms if they had not been screened. This implies overtreatment for the screening group, where some of the CRCs were unnecessarily discovered, which adds extra costs for the screening group that were not included in our estimates. To include this in the analysis, we would need data indicating the proportion of the population with undiagnosed CRC who die from non-CRC causes.

4.2 Strengths and weaknesses of the general model

The cycles in the model were set to one year. The precision level can be improved by shortening the cycle length, but this would make the model more complex and accentuate the trade-off between model complexity and accuracy. As a result of convex survival curves and half-cycle correction, we expected that this weakness would contribute to a slight overestimation of the mean survival.

The cohort used in the model was diagnosed at the age of 70 years. This age might have resulted in a higher survival rate than if we had used the average age in the OUS sample. In [5], the average age for stages I–IV at the year of diagnosis was 69.9, 72.3, 70.4, and 70.5 years, respectively, in the OUS sample. When comparing these patients with our 70-year-old patients (based on Weibull regressions), we found that the differences in overall 10-year survival were −0.2%, 4.2%, 0.7%, and 0.03%, respectively, for the four stages.

Another weakness of the analysis was that some of the data used were relatively old. The data on, for example, recurrence and resections were based on observations in the period 1993–2010, survival data in palliative phase were mainly based on data from 1995–2002, background mortality data were from 2009, and certain parts of the frequency estimates for metastatic surgery and medical treatment for complications were from 2003–2004. The estimates for the use of chemotherapy in the palliative phase and all unit costs were from 2011–2012. The validation of the model showed good correspondence with other models and studies from the same time period as our model [5]. The CRC mortality is currently lower than those estimated by the model, and the 5-year relative survival of CRC in Norway increased by 7.7 percentage points from the period 1998–2007 to 2013–2017 (Cancer in Norway 2017). We see the same trend for metastatic CRC in Norway, which does not seem to be in line with the trend in the Netherlands where Hamers et al. [39] concluded that the overall survival of real-life stage IV patients did not improve from 2008 to 2016.

The effects on total CRC cost of using relatively old data are uncertain because lower recurrence implies lower CRC cost due to fewer surgeries and reduced palliative chemotherapy, while increased use of more expensive drugs, particularly in the palliative phase, implies higher CRC cost. Further, if the threshold for

receiving surgical treatment for metastatic cancer has changed (most likely increased), our cost estimates would be too low, particularly for stage IV. In section 3.2.1, we showed the significance of changes in palliative chemotherapy and found that increased use of bevacizumab and EGFR-inh was of great importance for the overall treatment cost. It was therefore mitigating that the model's inputs for the palliative phase treatments were relatively up-to-date and based on expert opinions from 2011–2012. When developing the next version of the model, it will be important to update the input data.

Rectal and colon cancers are different with regard to survival and treatment. Therefore, optimally the model should provide results for colon and rectum cancer separately. Even though we had access to a high-quality dataset to estimate recurrence rates, the dataset was too small to identify recurrence rates for rectal and colon cancer separately. Hence, the model was based on rectum and colon jointly. Further, in addition to estimating the cost of CRC one of the objectives of this study was to estimate the effect of changing treatment strategies. In palliation, this would not distinguish between rectal and colon cancers. Nevertheless, in the model we adjusted for rectal and colon cancer by weighing the proportion of rectal versus colon cases in all health states. In addition, we accounted for the fact that more rectal cancer patients are eligible for radiotherapy and separated out colon and rectum cases concerning frequencies and unit cost of resections (see Table 1 in Online Resource 1) in each of the Dukes stages. Although the model does not provide separate results for rectal and colon cancer, the model is capable of calculating these separately by making a model run for each cancer if the required data are available.

Our study showed that the model's estimates of the total CRC cost are sensitive to changes in the chemotherapy treatment in the palliative phase. This means, for example, that in studies where we have to include future CRC costs (e.g., evaluation of screening), the uncertainty could be significant if the treatment strategies change a lot over time.

Future development of the general model should also include more detailed HRQoL measures and improvements to the palliative part of the model. In addition, the effect of CRC on HRQoL in the 'disease-free' health states should be considered.

5. Conclusions

The costs of CRC generally seem to be modest when comparing treatment cost and the number of years saved. The expected lifetime CRC costs increased with the stage of the disease at diagnosis and were higher among patient experiencing recurrence after a resection with a curative intent. Changes in the use of palliative chemotherapy had a major impact on the expected CRC costs. The current trend to use EGFR-inh more frequently as a 1st line of treatment and the increased use of palliative chemotherapy in the elderly can therefore have a profound impact on cost. Reducing the recurrence rate through improved surgical technique indicated a considerable cost-effectiveness potential.

The different applications of the model illustrate its flexibility and indicate how the general model might be used to evaluate a broad range of interventions, making the model useful for researchers, health policy makers, health authorities, innovators, and industry.

Abbreviations

5-FU/FA: Nordic FLv = 5-fluorouracil/folinic acid; CI: Confidence interval; COI: Cost-of-illness; CRC: Colorectal cancer; CrI: Credible interval; EGFR-inh: Epidermal growth factor receptor inhibitors (cetuximab/panitumumab); FLIRI: A combination of Irinotecan and 5-fluorouracil/folinic acid; FLOX: A combination of Oxaliplatin and 5-FU/FA; FOBTs: Faecal occult blood tests; HRQoL: Health-related quality of life; LYs: Life years; NPR: National Patient Registry; OUS: Oslo University Hospital; PSA: Probabilistic sensitivity analysis; PS: Patient performance status; QALY: Quality adjusted life years; WTP: Willingness to pay.

Online Resources

Online Resource 1: Data input to the base case model

Online Resource 2: Supplementary result for the base case model on chemotherapy costs

Online Resource 3: Sensitivity analysis for the base case model

Online Resource 4: Change in treatment strategies: data input and supplementary results

Online Resource 5: Productivity of CRC treatment

Tables and figures

Table 1 Overview of how decision-analytic models can be used to prioritise within and between diseases

Compare		Type of decision analysis	Users of the results
(i)	Between diseases	Burden of diseases and cost-of-illness	Politicians and health administrators
(ii)	Intervention strategies within a specific disease	Explorative analyses to identify intervention strategies with considerable potential gains in order to target research and investments: • Willingness to pay for specific health improvements • Healthcare savings and costs of specific health improvements • Healthcare costs of altered treatments	Researchers/innovators, inventors, and industry
(iii)	Specific treatments within and between intervention strategies	Evaluation of the cost-effectiveness of new interventions	Health administrators

Table 2 Expected lifetime costs (€), survival time, and QALYs for a 70-year-old CRC patient compared with the population without CRC.

	All stages	Stage I	Stage II	Stage III	Stage IV
Per cent in each stage at diagnosis	100.0	17.8	36.3	25.7	20.2
Total lifetime costs (€)	47,300	26,630	38,130	56,800	69,890
Types of treatment					
Preoperative diagnostics and staging (€)	2330	2160	2400	2680	1920
Surgery – major resection (€)	20,390	18,940	19,920	22,970	19,230
Surgery – other (€)	8230	1070	3240	9690	21,660
Adjuvant/neoadjuvant chemotherapy (€)	1530	30	600	4670	510
Radiotherapy (€)	1840	790	1800	3240	1080
Follow up, in total (€)	2060	790	3110	2880	230
Palliative chemotherapy (€)	10,920	2850	7070	10,680	25,260
Phases of the treatment					
Primary examination (€)	1880	1940	1870	1880	1860
Primary treatment (€)	28,830	19,290	21,800	34,990	42,050
Follow up first treatment (€)	1920	730	2950	2640	210
Examination and treatment of recurrence (1st year with diagnosed recurrence) (€)	3610	1750	4300	6360	500
Follow up after recurrence (€)	140	70	160	240	20
Palliative chemotherapy (€)	10,920	2850	7070	10,680	25,260
Treatment pathways					
Low estimate (Stage 1, no recur.) (€)		16,450	19,420	26,720	
High estimate (Full treatment including recurrence and bevacizumab) (€)		125,830	128,860	142,070	142,540
Survival: Life years and quality-adjusted life years (QALYs)					
Life years after diagnosis, undiscounted	9.3	14.0	11.5	9.0	1.5
Life years after diagnosis, discount. 4%	7.0	10.3	8.6	7.0	1.4
QALYs after diagnosis, discounted 4%	5.2	7.6	6.4	5.2	1.0
Life years lost, undiscounted	6.3	1.6	4.1	6.6	14.1
Life years lost, discounted 2%	5.1	1.2	3.2	5.2	11.6
Life years lost, discounted 4%	4.1	0.9	2.6	4.2	9.7
QALYs lost, discounted 4% [a]	3.7	1.4	2.6	3.8	7.9

[a] The alternative assumed for the CRC patients is that HRQoL is similar to average people of the same age. Therefore, we accounted for loss of HRQoL when living with CRC and loss of HRQoL caused by loss of LYs.

Table 3 Change in expected lifetime costs (€) for a 70-year-old CRC patient compared with the base case

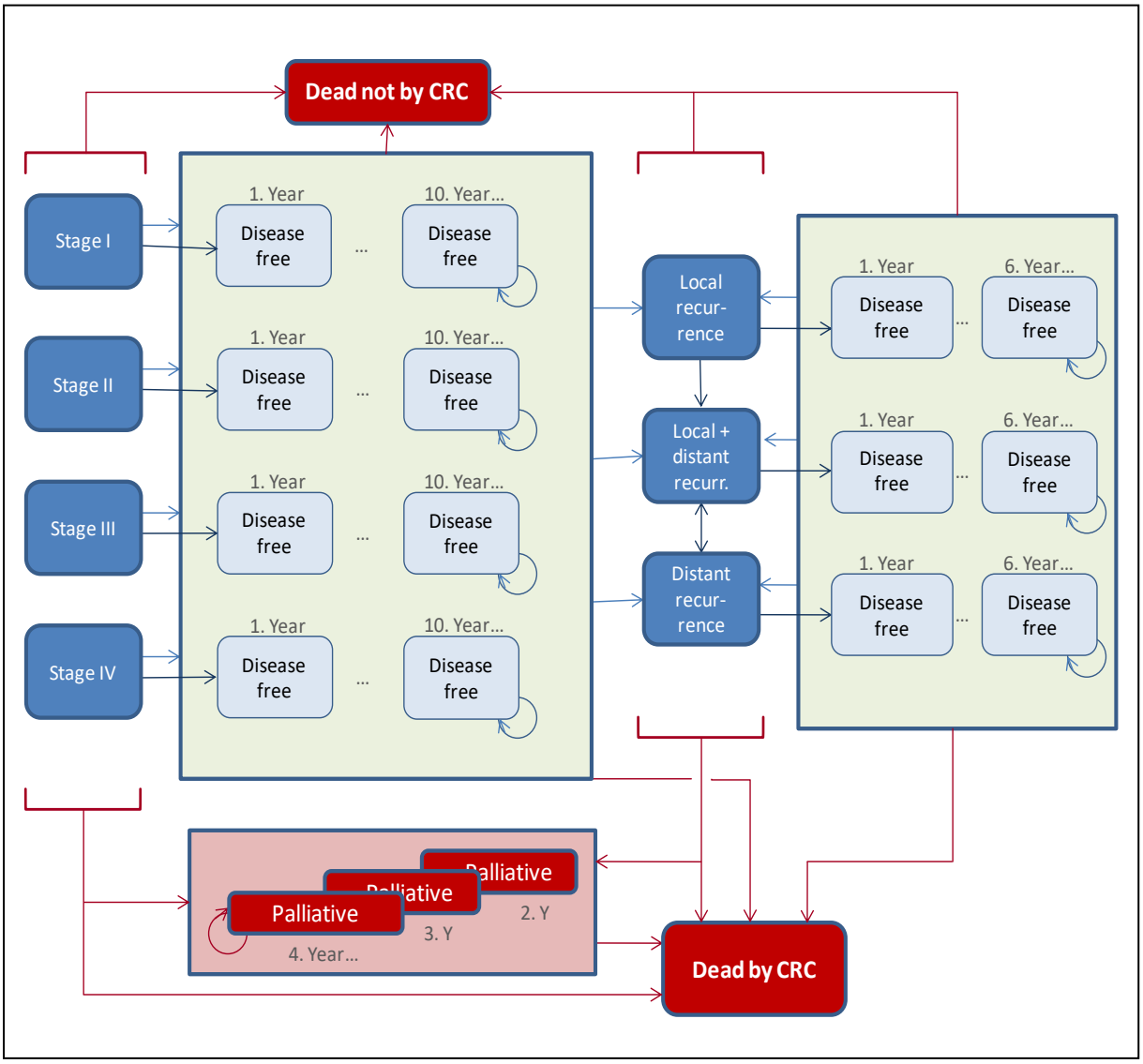
Selected palliative chemotherapy treatment alternatives	Cost change, %	Cost change, €
1. All patients on palliative chemotherapy receive bevacizumab	13.8	6520
2. No patients receive bevacizumab	-5.4	-2550
3. Patients who receive FLIRI/FLOX as the 1st line of treatment in the base case instead receive bevacizumab and FLIRI/FLOX	8.1	3830
4. Bevacizumab price from the pharmacy is reduced by 50%	-2.3	-1100
5. 'All' patients (including all elderly) not disease-free after treatment receive palliative chemotherapy	9.4	4450
6. All patients in scenario 5 above receive bevacizumab as the 1st line of treatment	28.8	13,630
7. Ten percentage points move from 5FU/FA-treatment (often old patients) to combination chemotherapy with bevacizumab	2.0	930
8. Ten per cent more CRC patients receive palliative chemotherapy among those diagnosed with stage IV or recurrence	2.3	1090

Table 4 Treatment strategies, assumptions, costs, quality-adjusted life years (QALYs), life years (LYs), and willingness to pay (WTP) per person. Discounting is 4%, and all numbers are in €

Intervention	Assumption	Costs saving (€)	QALYs	LYs	WTP (€)
Reduction in recurrence rate (per patient treated)	32.5% to 27.5% for stage I, II, and II in total.	2190	0.32	0.43	28,540
Primary prevention (per prevented CRC case)	One CRC case prevented	47,300	3.7	4.1	353,660
Screening with FOBTs, Denmark (UK)	See the stage migration in Table 2 in Online Resource 4	14.9 per screened individual (21.6) 7300 per CRC detected (10,306)			
Gain of CRC treatment in general (all stages, per treated)	See Online Resource 5	47,300	3.0	4.0	245,920 (Gain of €5.2 per € invested)

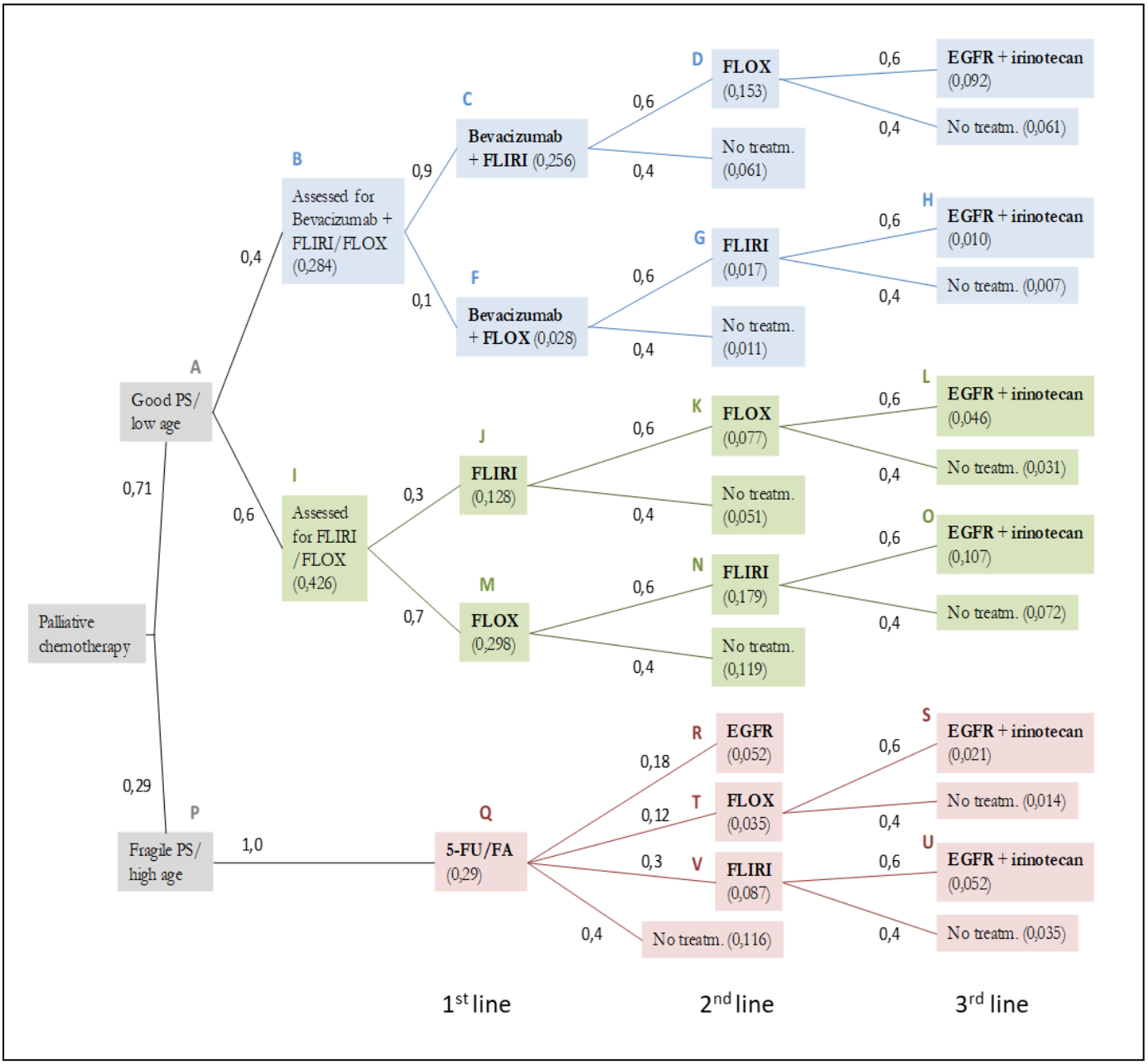
FOBTs: Faecal occult blood tests

Fig. 1 Illustration of how the patient can move from one state to another in the model.



Legend to Figure 1: Reproduced from [5) with kind permission from Sage publishers.

Fig. 2 The decision tree for palliative chemotherapy



Legend to Figure 2: Conditional probabilities without brackets. The numbers in brackets show the probabilities of patients receiving the treatment in the box given that the patients receive some kind of palliative treatment. 5-FU/FA: Nordic FLv = 5-fluorouracil/folinic acid; EGFR-inh: Epidermal growth factor receptor inhibitors (cetuximab/panitumumab); FLIRI: A combination of Irinotecan and 5-FU/FA; FLOX: A combination of Oxaliplatin and 5-FU/FA; PS: Patient performance status. Reproduced from (5) with kind permission from Sage publishers.

References

1. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiology Biomarkers & Prevention. 2010;19(8):1893-907.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer. 2013;49(6):1374-403.
3. Tarricone R. Cost-of-illness analysis. Health Policy. 2006;77(1):51-63.
4. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget Impact Analysis - Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in Health. 2014;17(1):5-14.
5. Joranger P, Nesbakken A, Hoff G, Sorbye H, Oshaug A, Aas E. Modeling and validating the cost and clinical pathway of colorectal cancer. Medical Decision Making. 2014.
6. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. Journal of Health Economics. 1997;16(1):33-64.
7. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G, editors. Methods for the Economic Evaluation of Health Care Programmes. Third ed: Oxford University Press; 2005.
8. Sjo OH, Lunde OC, Nygaard K, Sandvik L, Nesbakken A. Tumour location is a prognostic factor for survival in colonic cancer patients. Colorectal Disease. 2008;10(1):33-40.
9. Nesbakken A, Nygaard K, Westerheim O, Mala T, Lunde OC. Local recurrence after mesorectal excision for rectal cancer. European Journal of Surgical Oncology. 2002;28(2):126-34.
10. Aas E. Cost-effectiveness of screening for colorectal cancer with once-only flexible sigmoidoscopy and faecal occult blood test. Oslo University, Health Economics Research Programme; 2009.
11. Yabroff KR, Lawrence WF, Clauser S, Davis WW, Brown ML. Burden of Illness in Cancer Survivors: Findings From a Population-Based National Sample. Journal of the National Cancer Institute. 2004;2004/09/01:9.
12. Saarni SI, Härkänen T, Sintonen H, Suvisaari J, Koskinen S, Aromaa A, et al. The Impact of 29 Chronic Conditions on Health-related Quality of Life: A General Population Survey in Finland Using 15D and EQ-5D. Quality of Life Research. 2006;15(8):1403-14.
13. Health Do. Economic evaluation of health intervention - a guide. Oslo: The Norwegian Directorate of Health; 2012.
14. Finance Mo. Guid for cost-benefit analysis. Oslo: The Treasury Department; 2005.
15. Finance Mo. Principles and requirements for the preparation of socio-economic analyzes. In: Finance Mo, editor. Oslo: Ministry of Finance; 2014.
16. Razenberg LGEM, Creemers G-J, Beerepoot LV, Vos AH, van de Wouw AJ, Maas HAAM, et al. Age-related systemic treatment and survival of patients with metachronous metastases from colorectal cancer. Acta Oncologica. 2016;55(12):1443-9.
17. Sorbye H, Pfeiffer P, Cavalli-Björkman N, Qvortrup C, Holsen MH, Wentzel-Larsen T, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. Cancer. 2009;115(20):4679-87.
18. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut. 2012;61(7):1036-40.
19. RCPH. Screening for colorectal cancer in Vejle and Copenhagen county: Research Centre for Prevention and Health (RCPH); 2007.
20. Tappenden P, Chilcott J, Eggington S, Sakai H, Karnon J, Patnick J. Option appraisal of population-based colorectal cancer screening programmes in England. Gut. 2007;56(5):677-84.

21. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA: The Journal of the American Medical Association. 2000;284(15):1954-61.
22. Tappenden P, Eggington S, Nixon R, Chilcott J, Sakai H, Karnon J. Colorectal cancer screeing options appraisal - cost-effectiveness, cost-utility and resource impact of alternative screening options for colorectal cancer. School of Health and Related Researche (ScHARR), University og Sheffild; 2004.
23. Ladabaum U, Phillips KA. Colorectal cancer screening: Differential costs for younger versus older Americans. American journal of preventive medicine. 2006;30(5):378-84.
24. Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: Application to medicare enrollees diagnosed with colorectal cancer. Medical Care. 1999;37(12):1249-59.
25. Yabroff KR, Borowski L, Lipscomb J. Economic studies in colorectal cancer: Challenges in measuring and comparing costs. JNCI Monographs. 2013;2013(46):62-78.
26. Tilson L, Sharp L, Usher C, Walsh C, S W, O'Ceilleachair A, et al. Cost of care for colorectal cancer in Ireland: a health care payer perspective. The European Journal of Health Economics. 2012;13(4):511-24.
27. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, et.al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology. 2016;27(8).
28. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with ras wild-type metastatic colorectal cancer: Retrospective analyses of the crystal and fire-3 trials. JAMA Oncology. 2017;3(2):194-201.
29. Norderhaug I TH. Pasientvolum og kvalitet ved koloncancerkirurgi. Oslo: Nasjonalt kunnskapssenter for helsetjenesten; 2009.
30. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. Physical activity and survival after colorectal cancer diagnosis. Journal of Clinical Oncology. 2006;24(22):3527-34.
31. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. Journal of Clinical Oncology. 2006;24(22):3535-41.
32. Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. Physical activity and male colorectal cancer survival. Arch Intern Med. 2009;169(22):2102-8.
33. Lynch BM, Cerin E, Owen N, Aitken JF. Associations of leisure-time physical activity with quality of life in a large, population-based sample of colorectal cancer survivors. Cancer Causes & Control. 2007;18(7):735-42.
34. Haydon AM, MacInnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut. 2006;55(1):62-7.
35. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA: The Journal of the American Medical Association. 2007;298(7):754-64.
36. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. International Journal of Cancer. 2009;125(1):171-80.
37. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA: A Cancer Journal for Clinicians. 2012;62(4):242-74.
38. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. The American Journal of Clinical Nutrition. 2012;96(6):1346-53.
39. Hamers P, Bos ACRK, May AM, Punt CJA, Koopman M, Vink GR. Recent changes in overall survival of real-life stage IV colorectal cancer patients. Journal of Clinical Oncology. 2019;37(15_suppl):3522-.

Online Resource 1:

Data input to the base case model

Journal name: The European Journal of Health Economics.

Article title: Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach.

Authors: Paal Joranger, Arild Nesbakken, Halfdan Sorbye, Geir Hoff, Arne Oshaug, Eline Aas.

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Table 1 Frequency per-patient and values per-unit for primary treatments used in the base case model analysis. The frequencies show how many times an average patient with a certain diagnosis receives the listed treatment (see also the text). Costs are in 2011 €

Treatment first year after primary diagnosis (DRG, medical: M, surgical: S)	Row no.	Primary treatment stage				Unit cost (€)	Source
		I	II	III	IV		
Resection of primary tumour							
Colon resection, w (148, S)	1	.210	.280	.458	.443	23,913	OUS
Colon resection, n (149, S)	2	.300	.401	.192	.023	11,688	OUS
Rectal resection, w (146, S)	3	.267	.174	.218	.120	18,546	OUS
Rectal resection, n (147, S)	4	.221	.145	.119	.0	12,486	OUS
Non-resection surgery							
Endoscopic therapy colon; closure stoma, w (152, S)	5	.0	.0	.045	.026	9539	NPR
Endoscopic therapy colon; closure stoma, n (153, S)	6	.036	.036	.090	.026	6758	NPR
Endoscopic therapy rectum; TEM, w (157, S)	7	.0	.0	.0	.101	5519	OUS
Endoscopic therapy rectum; TEM, n (158, S)	8	.0	.0	.0	.034	2748	OUS
GI obstruction, w (180, S)	9	.0	.0	.0	.044	3939	OUS
GI obstruction, n (181, S)	10	.0	.0	.0	.015	2140	OUS
Endoscopic/other treatment							
Digestive malignancy, w (172, M)	11	.0	.107	.493	1.526	7526	NPR
Digestive malignancy, n (173, M)	12	.0	.0	.164	.184	4409	NPR
Aftercare and rehabilitation (465)	13	.0	.0	.030	.553	6207	NPR
Endoscopic insertion of stent to Gastro; tract, short therapy (703O)	14	.0	.0	.0	.008	1310	OUS
Treatment for metastasis							
Resection							
Liver metastasis resec., w (191B, S)	15	.0	.0	.0	.125	26,528	Source a
Lung metastasis resection (75, S)	16	.0	.0	.0	.019	18,968	Source b
Non-surgical supportive treatment and care							
Liver metastasis (203, M)	17	.0	.0	.0	.188	6468	NPR, exp
Lung metastasis (82, M)	18	.0	.0	.0	.075	7664	NPR, exp
Chemo- and radiotherapy							
Radiotherapy (409E, M)	19	.033	.075	.147	.056	645 *	Source c, exp
Palliative chemotherapy (M)	20	.0	.0	.0	.610	20,183 †	Source d
Adjuvant chemotherapy (M)	21	.0	.054	.535	.05	8677/ 7494	Source e

Note: *w*=with complications or co-morbidities; n=without complications or co-morbidities; exp=Expert opinion; OUS=observational study at Oslo University Hospital – Aker; NPR=National Patient Register based on data organized by Aas (1); *=costs per visit at hospital for radiotherapy; †=costs in the first year of palliative treatment; Source a=(2), (20), (3), (4); Source b=(2), (4); Source c=(5, 6), exp.; Source d=(5, 7-10); Source e=(5, 7-10). Reproduced from (11) with the kind permission of Sage publishers.

References

1. Aas E. Cost-effectiveness of screening for colorectal cancer with once-only flexible sigmoidoscopy and faecal occult blood test. Oslo University, Health Economics Research Programme; 2009.

2. Körner H, Söreide K, Stokkeland P, Söreide J. Systematic follow-up after curative surgery for colorectal cancer in Norway: A population-based audit of effectiveness, costs, and compliance. Journal of Gastrointestinal Surgery. 2005;9(3):320-8.
3. SøreideJ A, Eiriksson K, Sandvik O, Viste A, Horn A, Johnsen G, et al. Kirurgisk behandling av levermetastaser fra kolorektal kreft. Tidsskr Nor Legeforen 2008;128(1):50-3.
4. Kobayashi H, Mochizuki H, Sugihara K, Morita T, Kotake K, Teramoto T, et al. Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer: A multicenter study. Surgery. 2007;141(1):67-75.
5. Delcò F, Egger R, Bauerfeind P, Beglinger C. Hospital health care resource utilization and costs of colorectal cancer during the first 3-year period following diagnosis in Switzerland. Alimentary Pharmacology & Therapeutics. 2005;21(5):615-22.
6. Sorbye H, Pfeiffer P, Cavalli-Björkman N, Qvortrup C, Holsen MH, Wentzel-Larsen T, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. Cancer. 2009;115(20):4679-87.
7. van Steenbergen L, Elferink M, Krijnen P, Lemmens V, Siesling S, Rutten H, et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. Annals of Oncology. 2010;21(11):2206-12.
8. Lemmens V, de Haan N, Rutten H, Martijn H, Loosveld O, Roumen R, et al. Improvements in population-based survival of patients presenting with metastatic rectal cancer in the south of the Netherlands, 1992–2008. Clinical and Experimental Metastasis. 2011;28(3):283-90.
9. Khattak MA, Townsend AR, Beeke C, Karapetis CS, Luke C, Padbury R, et al. Impact of age on choice of chemotherapy and outcome in advanced colorectal cancer. European Journal of Cancer. 2012;48(9):1293-8.
10. Jacob S, Ng W, Asghari R, Delaney GP, Barton MB. Estimation of an optimal chemotherapy utilisation rate for colon cancer: An evidence-based benchmark for cancer care. European Journal of Cancer. 2009;45(14):2503-9.
11. Joranger P, Nesbakken A, Hoff G, Sorbye H, Oshaug A, Aas E. Modeling and validating the cost and clinical pathway of colorectal cancer. Medical Decision Making. 2014.

Online Resource 2:

Supplementary results for the base case model on chemotherapy costs

Journal name: The European Journal of Health Economics.

Article title: Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach.

Authors: Paal Joranger, Arild Nesbakken, Halfdan Sorbye, Geir Hoff, Arne Oshaug, Eline Aas.

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Table 1 The costs of different components of the palliative chemotherapies (2016-euro)

Components in the treatment	5-FU/ FA	Bevaci-zumab+ FLIRI	Bevaci-zumab+ FLOX	FLIRI 1st line	FLIRI 2nd line	FLOX 1st line	FLOX 2nd line	EGFR + irinotecan ≤75 year	EGFR + irinotecan, >75 year
Medicine (from pharmacy)	3507	37,261	36,166	6590	4793	5786	4208	35,143	33,915
Administered in hospital	545	1362	1362	500	363	999	727	2 452	2452
CT-scanning	1 171	1343	1343	1073	781	1073	781	3 222	3222
Out-patient consultation	1704	2088	2088	1576	1192	1576	1192	2472	2472
Side effects*	1276	1934	1934	1220	1053	1220	1053	1762	1762
Sum cost	8,202	43,988	42,892	10,959	8 182	10,655	7,960	45,051	43,823

* Side effects include sepsis, intestine perforation, arterial thromboembolism and medicine for nausea. Diarrhea is included in another part of the model.

Table 1 is based on Table 9 in Appendix 1 of Joranger et al (1). The estimates are changed from 2011-euro in Table 9 to 2016-euro in Table 1 above, and we have added the column "EGFR + irinotecan, >75 year".

Table 2 Distribution of expected costs (percent) for an average group of patients receiving palliative chemotherapy

Scenarios	1. line	2. line	3. line	All lines
Bevacizumab og FLIRI, FLOX, EGFR-inh (C, D, E in Figure 2 in the main text)	27.5	3.0	10.1	40.7
Bevacizumab, og FLOX, FLIRI, EGFR-inh (F, G, H)	3.0	0.3	1.1	4.5
FLIRI, FLOX, EGFR-inh (J, K, L)	3.4	1.5	5.1	10.0
FLOX, FLIRI, EGFR-inh (M, N, O)	7.8	3.6	11.8	23.2
5-FU, EGFR-inh (Q, R)	1.7	5.6	0.0	7.3
5-FU, FLOX, EGFR-inh (Q, T, S)	1.2	0.7	2.2	4.1
5-FU, FLIRI, EGFR-inh (Q, V, U)	2.9	1.7	5.6	10.3
Sum costs all scenarios	47.5	16.4	36.0	100.0

EGFR-inh = Epidermal Growth Factor Inhibitor.
Note: The scenarios are shown in Fig. 2 in the main text.

In Table 2, percentages were estimated in the following way for patients receiving some kind of chemotherapy in the palliative phase: The expected cost for each chemotherapy regimen was estimated by multiplying the probability (in parentheses) of receiving the various treatments (given in Figure 2) with the sum costs of the respective chemotherapy regimens given in Table 1 above. Then, we estimated the percentage each chemotherapy regimen contributed to the total cost of the average patient receiving some kind of chemotherapy in the palliative phase, by dividing the estimated expected cost for each chemotherapy regimen with the expected total chemotherapy treatment cost for these CRC patients in palliative phase (€40,850 per patient). E.g. the percentage contribution for "Bevacizumab + FLIRI" in 1st line was estimated in this way: ((0,2556 x €43,988) / €40,850) x 100 = 27,5 percent.

Table 3 Total treatment costs per patient when receiving all chemotherapy in the treatment scenario (undiscounted)

Treatment scenario	Costs per patient (€)
Bevacizumab and FLIRI, FLOX, EGFR-inh + irinotecan (C, D, E in Figure 2 in the main text)	97,000
Bevacizumab and FLOX, FLIRI, EGFR-inh + irinotecan (F, G, H)	96,130
FLIRI, FLOX, EGFR-inh + irinotecan (J, K, L)	63,970
FLOX, FLIRI, EGFR-inh + irinotecan (M, N, O)	63,890
5-FU/FA, EGFR-inh + irinotecan (Q, R)	52,030
5-FU/FA, FLOX, EGFR-inh + irinotecan (Q, T, S)	59,990
5-FU/FA, FLIRI, EGFR-inh + irinotecan (Q, V, U)	60,210

References

1. Joranger P, Nesbakken A, Hoff G, Sorbye H, Oshaug A, Aas E. Modeling and validating the cost and clinical pathway of colorectal cancer. Medical Decision Making. 2014.

Online Resource 3:

Sensitivity analysis for the base case model

Journal name: The European Journal of Health Economics.

Article title: Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach.

Authors: Paal Joranger, Arild Nesbakken, Halfdan Sorbye, Geir Hoff, Arne Oshaug, Eline Aas.

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One-way and multi-way sensitivity analyses

We performed a one-way sensitivity analysis as shown in Figure 1. For the blue columns, we increased the relevant parameter by 20%. The most important parameter was selected and shown in the figure. These columns can be analysed based on price change or change in the use of resources. The green columns show selected changes in the parameters normally decided by the government to be partly empirically based, and the dark grey columns represent different scenarios (see more in Table 3 in the main text and Table 1 in Online Resource 4).

From the group to the left in Figure 1 ('Discount rate'), we see that the costs for an average CRC patient change approximately +/-1% if the discount rate changes from 4% to 3% (the 3rd green bar) or 5% (the 2nd green bar), which is normally the alternative value of the rate. The last green columns from the left show that the costs change by 3.5% if the value per DRG increases by 5%.

In the blue column, resection of the colon (5.7%) and rectum (2.5%) have the largest effect on the total costs (group 2). Our data are reliable regarding the probability of different CRC patients having these resections, so the increase of 20% seems to be large compared to the real uncertainty for these parameters. The costs estimate per resection is based on the DRG score system which is a common method in health evaluation today, but it is nevertheless criticized for having low reliability (Drummond et al., 2005, p. 59).

In group 3, we see that a 20% increase for all radiation (0.8%) or for all kinds of neoadjuvant or adjuvant chemotherapy treatments (0.7%) has less than a 1% effect on the total CRC costs for all stages.

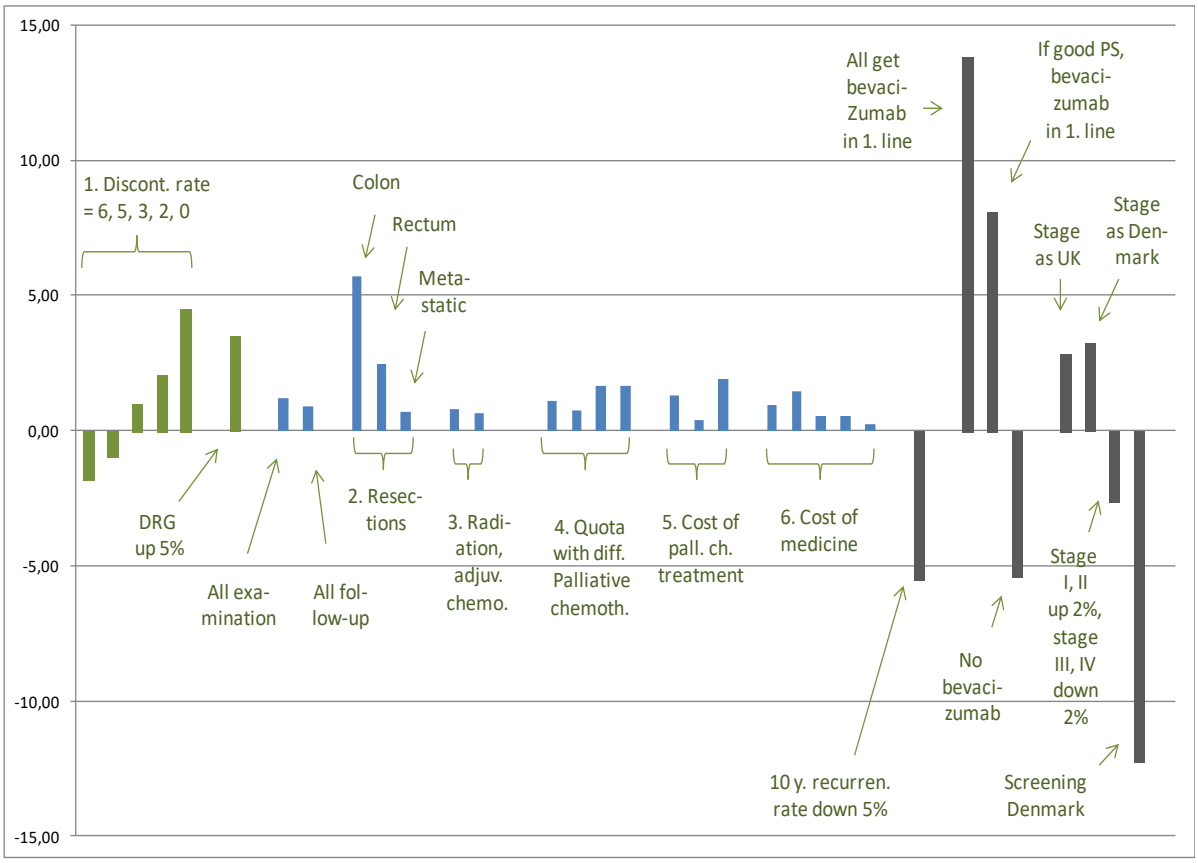

Fig. 1 Percentage change in total costs (all stages) when parameters are increased by 20% (the blue column) or changed as shown in the figure and in the text

For group 4, we analyse the effect of changing the probability of receiving a certain treatment by 20% and see that the results are affected by more than 1% for three of the elements. There is a lack of relevant statistics for this parameter, and we rely partly on expert opinion. Furthermore, this parameter does change over time. Some possible effects of change are shown by the three dark grey columns. Palliative chemotherapy seems to be an important area for controlling uncertainty in the costs analysis because of both the scarcity of data and the changing use of expensive drugs.

For ‘6. Costs of medicine’ (price at pharmacy), we expect the parameter to be close to the prices the hospital paid for medicine in 2011. However, these prices often change over time and contribute important uncertainty to the study of long time horizons (study of screening).

The first three dark grey columns to the right show the effect on the costs when different transition probabilities are changed. The first column shows a 5% decrease in the 10-year recurrence rate, reducing the costs by 5.3% for stages I, II, and III as a whole. This seems to be both a test of the uncertainty about the level of the parameters’ current value and a relevant change in the real value of recurrence for future years.

In addition, the stage distribution will influence the all-stage CRC costs. If we increase stages I and II by two percentage points and reduce stage III and IV by two percentage points, the costs will decrease by 2.6%. Furthermore, if we change our distribution to be similar to the control group in the UK (Nottingham) or the Danish study, then the costs will increase by 2.8% and 3.2%, respectively. This indicates that comparing all-stage CRC costs between populations can be disturbed by a different stage distribution. This can be important when some countries have screening programmes and others do not. The last column shows the costs reduction (12.2%) if the stage distribution is changed to the screening group in the Danish study (1).

Generally, the costs results seemed to be sensitive to changes in treatment algorithms (e.g., palliative chemotherapy and screening). This is especially important for evaluation studies with long time horizons such as for CRC screening and prevention. Due to a lack of data and continuous changes in the use of expensive chemotherapies, uncertainty in palliative chemotherapy seems to be an important area to address.

Probabilistic sensitivity analysis of expert opinions

The probability of receiving R0 resection after recurrence and all the conditional probabilities on the right side of box A and Q in Figure 2 in the article were based on experts' opinions. According to Weinstein et al. (2003), ‘Expert opinion is a legitimate method for assessing parameters, provided either that these parameters are shown not to affect the results importantly or that a sensitivity analysis is reported on these

parameters with a clear statement that results are conditional upon this (these) subjective estimate(s)'. To determine whether the parameters assessed using expert opinion significantly affected the results, we performed one-way deterministic sensitivity analysis for all these individual parameters and for approximately 100 other parameters to which we thought the results could be sensitive. Figure 1 shows the effect of the most important parameters (blue columns). More details of the parameters used in the palliative model are shown in Figure 2 in the main text. Based on these deterministic sensitivity analyses, we found that the parameters assessed by experts (the parameters referred to above) do not substantially affect the results.

So far, we have presented and discussed the effects of the parameters one by one. However, what about the total effect of simultaneous uncertainty in all the parameters based on expert opinion? To illustrate this, we performed a probabilistic sensitivity analysis (PSA) in which all these parameters were given distributions (Beta) with an upper CI 30% higher than the mean value. For the costs estimate, we see the results in Figure 2, where the 95% CrI is +2.8% and -2.7% of the mean. In Figure 3, we see the effect on survival, where the 95% CrI is +0.48% and -0.56% of the mean. *We argue that this implies that uncertainties related to the use of expert opinion were not important to the results.*

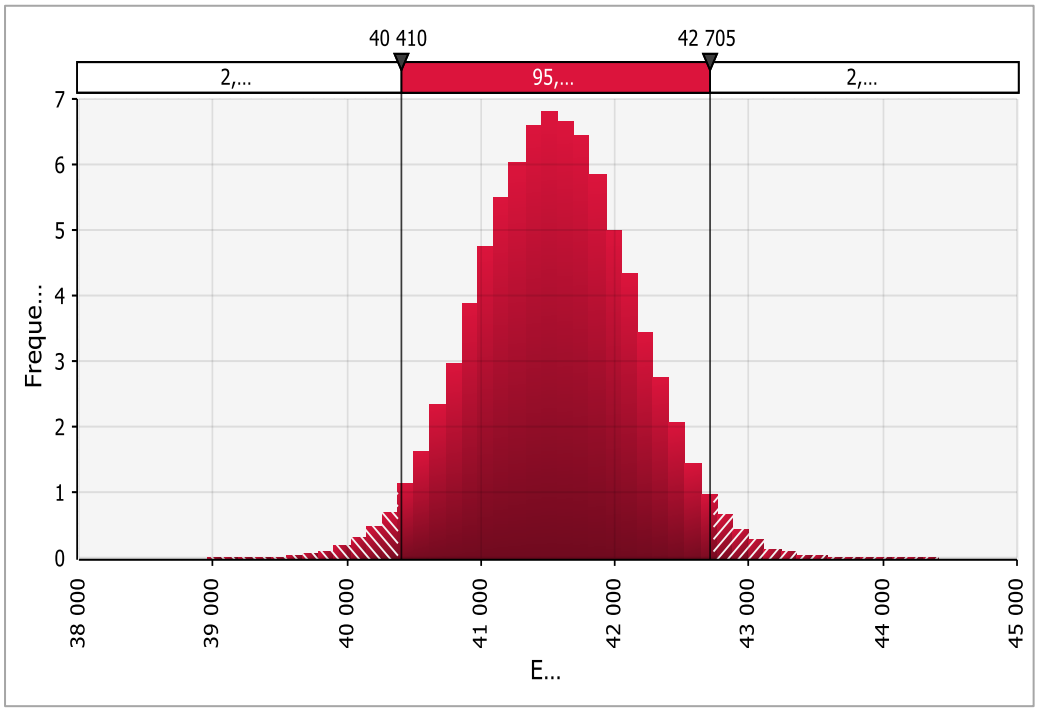

Fig. 2 Uncertainty in costs estimates (2011 €)

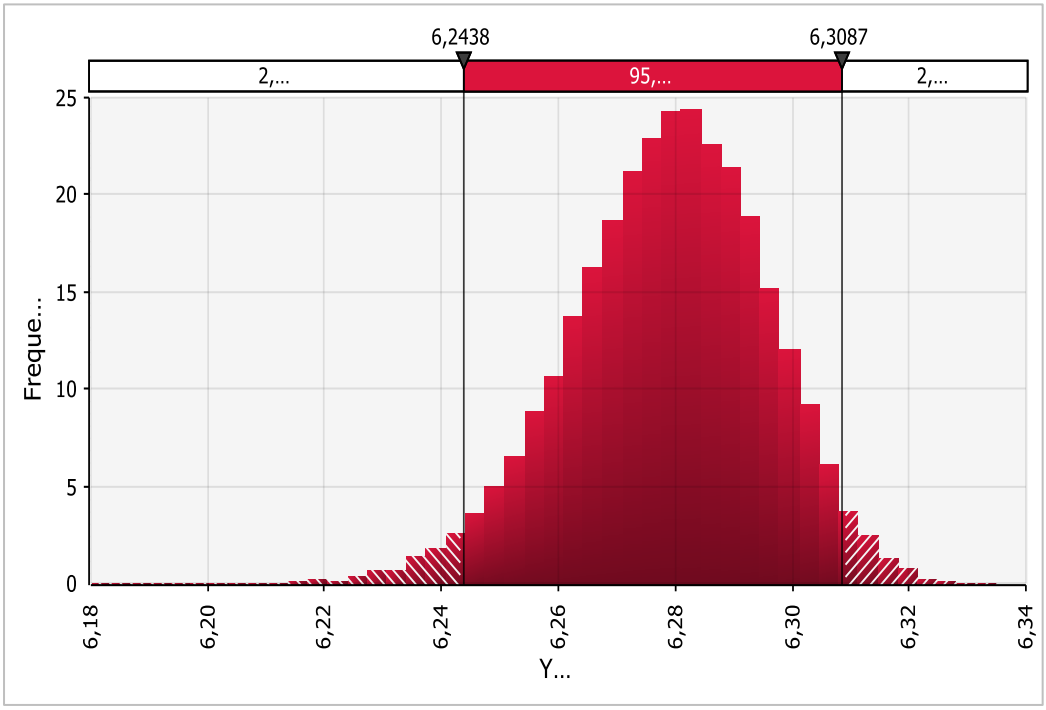

Fig. 3 Uncertainty in survival estimates

References

1. RCPH. Screening for colorectal cancer in Vejle and Copenhagen county: Research Centre for Prevention and Health (RCPH); 2007.

Online Resource 4:

Change in treatment strategies: data input and supplementary results

Journal name: The European Journal of Health Economics.

Article title: Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach.

Authors: Paal Joranger, Arild Nesbakken, Halfdan Sorbye, Geir Hoff, Arne Oshaug, Eline Aas.

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Change in the costs of palliative chemotherapy

Table 1 Change for an average CRC patient when increasing the input variable

Treatment	20% increase		0.1 quota increase [a]
	Per cent change	Costs change	Per cent change
Change in the probability of receiving			
5-FU/FA in 1st line of treatment (5FU/FA-scenario)	-0.48	-230	-0.83
Chemotherapy, 2nd line of treatment in the '5-FU/FA-scenario'	0.72	340	0.60
Bevacizumab, 1st line of treatment, assumed in 'no-5-FU/FA-sc'	1.08	510	1.35
Chemotherapy, 2nd line of treatment, assumed in 'no-5-FU/FA-sc'	1.66	790	1.38
Chemotherapy (EGFR-inh + irinotecan), 3rd line of treatment	1.63	770	1.36
Change in costs for the treatment			
5-FU	0.27	130	
Bevacizumab+FLIRI	1.29	620	
Bevacizumab+FLOX	0.14	70	
FLIRI 1st line of treatment	0.16	80	
FLOX 1st line of treatment	0.37	170	
EGFR-inh (+ irinotecan)	1.89	890	
Change in the costs of the medicine			
Bevacizumab	0.92	430	
FLIRI	0.51	240	
FLOX	0.54	250	
EGFR-inh (+ irinotecan)	1.47	690	
5-FU/FA	0.24	110	

[a]10 percentage points increase

To show the importance of uncertainty in the input data, we estimated the effect of changes in both prices and probabilities (Table 1). Most sensitive to the 20% change in treatment costs were the EGFR-inh + irinotecan treatment with a 1.89% change (€780) and the '*bevacizumab + FLIRI*' treatment with a 1.29% change (€540).

When we only considered a 20% increase in drug costs from the pharmacy, EGFR-inh + irinotecan had a 1.47% change (€610), and bevacizumab had a 0.92% change (€380). The price of 5-FU/FA was least sensitive (0.24%, €100) to a 20% change.

Input data to the screening analysis

Assuming that a person has CRC, Table 2 shows the probability of being diagnosed at the different stages of CRC. The data were based on one study from Denmark and one from the UK (Nottingham) (1, 2).

Table 2 How CRC patients are distributed in the screened and control groups

	Denmark		UK (Nottingham)	
	Screened	Control	Screened	Control
Stage I	0.370	0.148	0.506	0.151
Stage II	0.277	0.338	0.205	0.346
Stage III	0.272	0.300	0.241	0.285
Stage IV	0.081	0.214	0.048	0.218

References

1. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut. 2012;61(7):1036-40.
2. RCPH. Screening for colorectal cancer in Vejle and Copenhagen county: Research Centre for Prevention and Health (RCPH); 2007.

Online Resource 5:

Productivity of CRC-treatment

Journal name: The European Journal of Health Economics.

Article title: Survival and costs of colorectal cancer treatment and effects of changing treatment strategies - a model approach.

Authors: Paal Joranger, Arild Nesbakken, Halfdan Sorbye, Geir Hoff, Arne Oshaug, Eline Aas.

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To estimate the gain in life expectancy brought on by CRC treatment, we need to know the life expectancy with and without treatment. The mean life expectancy with treatment is estimated by the CRC model and can be found in Table 2 in the main text. In this appendix, we present the methods for the estimation of life expectancy for patients *without* treatment.

To estimate life expectancy for patients *without* treatment, i.e., the contrafactual of those with treatment, we applied the model illustrated in Figure 1. The individuals are assigned to stages I, II, III, or IV according to what is observed for symptomatic cancers in the general population. Based on this assignment, the individuals do not receive treatment and progress to more severe stages. For example, a patient in stage II could remain there, progress to stage III, or die from causes other than CRC. A patient in stage III could similarly stay, progress to stage IV, or die from causes other than CRC. A patient in stage IV could stay, die from CRC, or die from causes other than CRC. Hence, patients could die from CRC only in stage IV. We follow the patients from 70 years of age until they are 100 years old or deceased. The cycle length was one year.

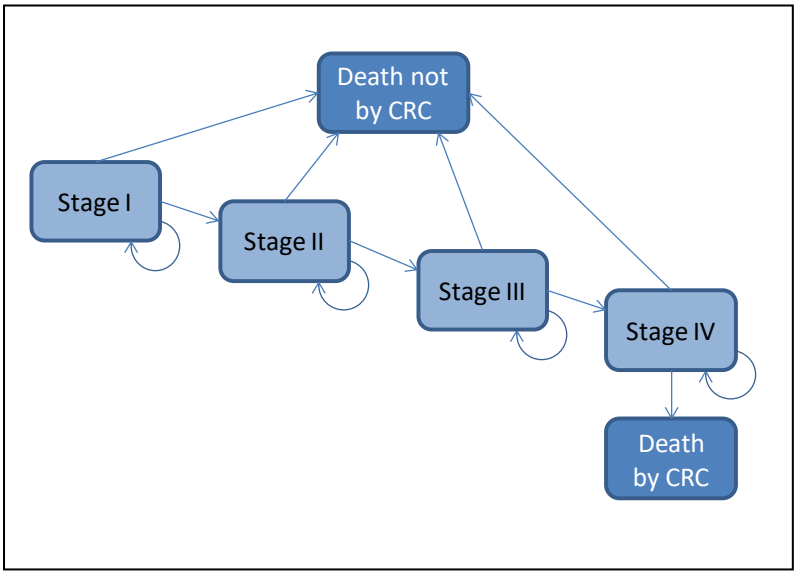

Fig. 1 The Markov model estimating survival for untreated patients

The model was based on the following assumptions:

1. The transition probabilities (and CI used in the PSA) from one stage to another: Stage I to stage II was 0.583 (0.3-0.9) per year; stage II to stage III was 0.656 (0.3–0.9), and stage III to stage IV was 0.747 (0.31–0.85).
2. We assumed no CRC deaths when the patients were in stages I-III.
3. For all years in stages I-III, we assumed the annual probability of non-CRC death to be 0.0199.
4. The transition probabilities for staying in the same state for another year were 0.397, 0.324, 0.233, and 0.418 for stages I, II, III, and IV, respectively.
5. For patients in stage IV, we assumed the total annual probability of non-CRC and CRC death to be 0.582.
6. To discount survival, we used a 4% annual discount rate.

The assumptions in point 1 are based on the literature, where the transition probabilities are estimated using calibration methods (1-3). In point 3, the parameter is based on life tables for Norway and is the average annual probability of non-CRC death for ages 70-74 years. If we perform a simulation in which the patients are starting in all four stages (I-IV), then 68.9% of the population with CRC will die from CRC or something else during these four years.

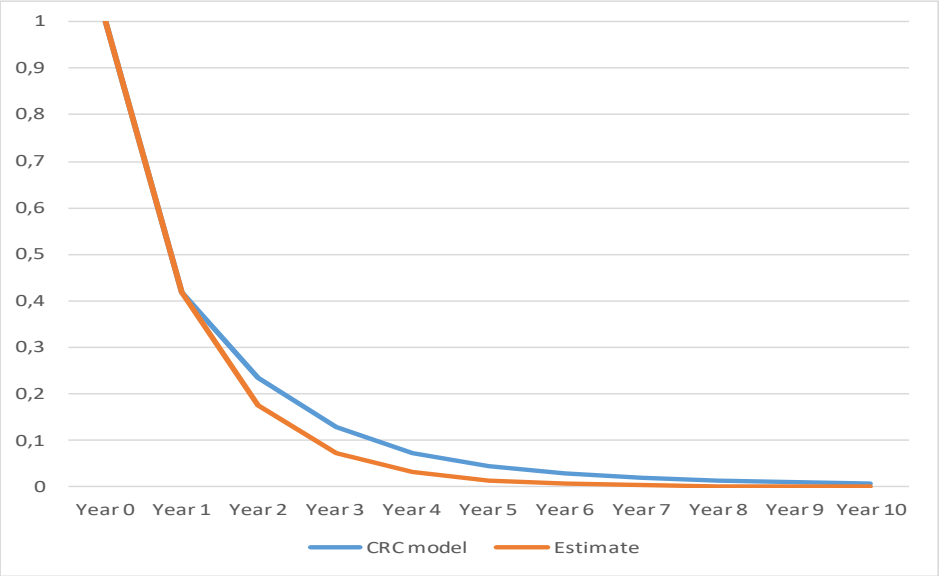

Fig. 2 Survival for persons with CRC stage IV (CRC model = treated, Estimate = untreated)

In point 5, we assume that annual survival was the same for untreated people in stage IV as this is the survival rate in the CRC model the first year after the patients were diagnosed as stage IV. In year 2 or later, the CRC model (diagnosed and treated patients) predicts a higher survival rate than we assumed for the untreated persons (see Figure 2). We will argue that we have made conservative assumptions about the difference in survival between treated and untreated patients in stage IV, and this will reduce the estimated gain to society from CRC treatment.

In Table 1, we show an example of simulations of survival with and without discounting. Table 2 shows the survival rate under different combinations of CRC stages for the patients and the gain to society per Euro spent on CRC treatment.

Table 1 Annual survival rate for untreated people with CRC

	Stage I	Stage II	Stage III	Stage IV	Deceased	Persons survived	Pers. surv. discounted
Year 0, start	17.800	36.300	25.700	20.200		100.000	100.000
Year 1	7.068	22.142	29.803	27.642	13.344	86.656	83.323
Year 2	2.807	11.297	21.472	33.817	30.606	69.394	64.159
Year 3	1.115	5.298	12.416	30.176	50.996	49.004	43.565
Year 4	0.443	2.367	6.370	21.888	68.933	31.067	26.556
Year 5	0.176	1.025	3.037	13.907	81.854	18.146	14.914
Year 6	0.070	0.435	1.381	8.082	90.033	9.967	7.877
Year 7	0.028	0.182	0.607	4.410	94.774	5.226	3.971
Year 8	0.011	0.075	0.261	2.297	97.357	2.643	1.931
Year 9	0.004	0.031	0.110	1.155	98.700	1.300	0.913
Year 10	0.002	0.013	0.046	0.565	99.375	0.625	0.422
Year 11	0.001	0.005	0.019	0.270	99.705	0.295	0.192
Year 12	0.000	0.002	0.008	0.127	99.863	0.137	0.086
Year 13	0.000	0.001	0.003	0.059	99.937	0.063	0.038
Year 14	0.000	0.000	0.001	0.027	99.971	0.029	0.017
Year 15	0.000	0.000	0.001	0.012	99.987	0.013	0.007
Year 16	0.000	0.000	0.000	0.005	99.994	0.006	0.003
Year 17	0.000	0.000	0.000	0.002	99.997	0.003	0.001
Year 18	0.000	0.000	0.000	0.001	99.999	0.001	0.001
Year 19	0.000	0.000	0.000	0.000	100.000	0.000	0.000
Year 20-30	…	…	…	…	…	…	…
Years survived, mean (half-cycle corrected)						3.240	2.980

Note: In this simulation, 100 theoretical patients were dispersed in all CRC stages according to how the treated patients are dispersed between stages when they are diagnosed.

Table 2 Difference in survival and gain to society between CRC treatment and no CRC treatment

	All stages	All-stage CrI percentile Lower 2.5%	Upper 97.5%	Stages I-III	Stage I	Stage II	Stage III
A. Estimated LYs and QALYs after diagnosis, without treatment:							
LYs not discounted	3.25	2.99	4.88	3.76	5.38	3.87	2.48
Lys discounted	2.98	2.77	4.24	3.44	4.79	3.55	2.34
QALYs not discounted	2.41	2.21	3.61	2.78	3.98	2.86	1.84
QALYs discounted	2.21	2.05	3.14	2.55	3.54	2.63	1.73
B. LYs or QALYs gained if treated (survival with treatment - A):							
LYs not discounted	6.05	4.42	6.31	7.49	8.62	7.63	6.52
LYs discounted	4.02	2.76	4.23	5.00	5.51	5.05	4.66
QALYs not discounted	4.48	3.27	4.67	5.54	6.38	5.65	4.82
QALYs discounted	2.97	2.04	3.13	3.70	4.08	3.74	3.45
C. Health gain estimated in Euros (B x WTP per QALY):							
LYs not discounted	501,350	366,350	522,440	620,170	713,490	631,880	540,110
LYs discounted	332,910	228,880	350,280	413,770	456,090	418,010	386,160
QALYs not discounted	370,940	270,760	386,680	458,710	528,260	460,370	399,100
QALYs discounted	245,920	168,910	259,160	306,360	337,820	309,670	285,660
D. Gain in Euros to society per Euro used for treatment (C / costs of CRC treatment):							
LYs not discounted	10.6	7.8	11.1	14.9	26.8	16.6	9.5
LYs discounted	7.0	4.8	7.4	9.9	17.1	11.0	6.8
QALYs not discounted	7.8	5.7	8.2	11.0	19.8	12.1	7.0
QALYs discounted	5.2	3.6	5.5	7.4	12.7	8.1	5.0

Note: *CrI*=Credible interval, *LY*=life years.

The uncertainty about the parameters was assumed to be large for the transition probabilities between stages, as shown in point 1 above. To handle this, we used a PSA to estimate the credibility intervals for mean survival without treatment. We used the range shown in point 1 above as the 95% confidence interval (CI) and used 0.36–0.48 as the 95% CI for the probability per year of dying when remaining in stage IV. Based on Tappenden et al. (3), we chose a uniform distribution. The results from this PSA can be seen as credibility intervals (CrIs) in Table 2 and as distributions in Figures 3 and 4. Using the upper level of survival for untreated patients in the analysis (all stages) resulted in a gain to society of €3.6 per Euro spent on treatment when discounting the QALYs and not discounting 5.7.

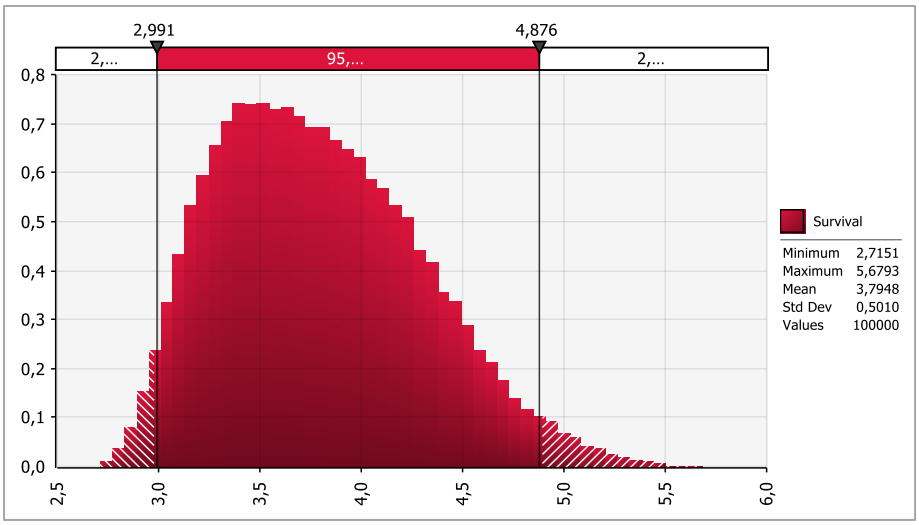

Fig. 3 Survival if patients are not treated and if the survival time is not discounted

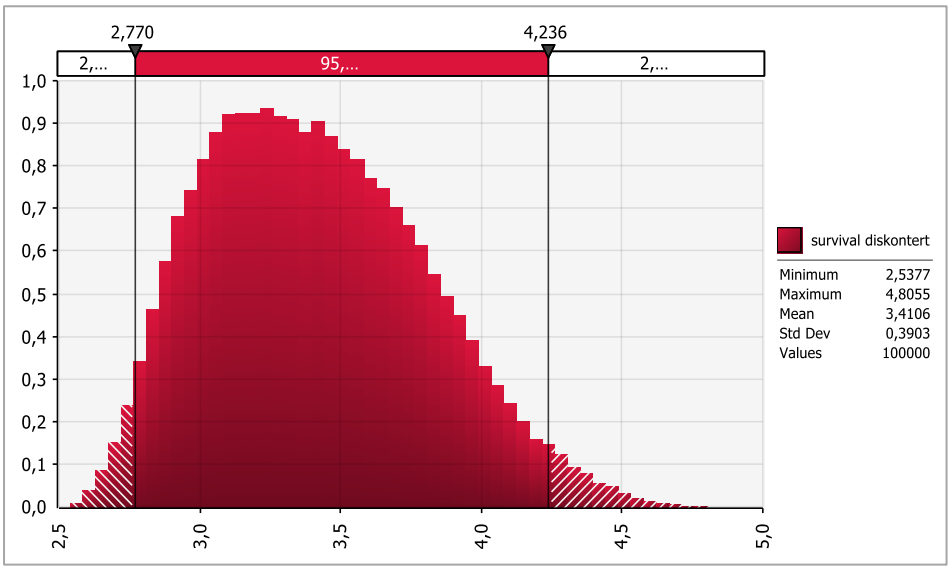

Fig. 4 Survival if patients are not treated and if the survival time is discounted

References

1. Tappenden P, Chilcott J, Eggington S, Sakai H, Karnon J, Patnick J. Option appraisal of population-based colorectal cancer screening programmes in England. Gut. 2007;56(5):677-84.
2. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. JAMA: The Journal of the American Medical Association. 2000;284(15):1954-61.
3. Tappenden P, Eggington S, Nixon R, Chilcott J, Sakai H, Karnon J. Colorectal cancer screeing options appraisal - cost-effectiveness, cost-utility and resource impact of alternative screening options for colorectal cancer. School of Health and Related Researche (ScHARR), University og Sheffild; 2004.