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Modeling and Validating the Cost and Clinical Pathway of Colorectal Cancer

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Abstract

Background: Cancer is a major cause of morbidity and mortality, with colorectal cancer (CRC) being the third most common cancer in the world. The estimated costs of CRC treatment varies considerably, and if CRC costs in a model are based on empirically estimated total costs of stage I, II, III or IV treatments, then they lack some flexibility to capture future changes in CRC treatment.

Objectives: The purpose was in a transparent and reproducible way (i) to describe how to model CRC costs and survival and (ii) to validate the model.

Design: We applied a semi-Markov model with 70 health states and tracked age and time since specific health states (using tunnels and three dimensional data matrix).

Data source: The model parameters are based on an observational study at Oslo University Hospital (2049 CRC-patients), the National Patient Register, literature and expert opinion.

Target population: Patients diagnosed with colorectal cancer (CRC).

Time period: The model followed the patients diagnosed with CRC from the age of 70 until death or 100 years.

Perspective: The health care payers' perspective.

Results/validation: The model was validated for face-, internal-, cross- and external validity. The validation showed a satisfactory match with other models and empirical estimates for both cost and survival time, without any preceding calibration of the model.

Conclusions: The model can address a range of CRC-related themes (general model) like survival and evaluation of the cost of treatment and prevention measures; predictions from intermediate to final outcomes; estimate changes in resource use and costs due to changing guidelines and adjusting for future changes in treatment and trends over time. The model is adaptable to other populations.

1 Introduction

Cancer is a major cause of morbidity and mortality in the Western world, and colorectal cancer is the second most common cancer in women and third in men(1). The 5-year relative survival rates is 47% in Europe and 60% in US(2). The economic burden of cancer is expected to increase in the future, partly due to changing demographics and the introduction of new and resource-demanding treatments and screening methods. Thus, it is important to monitor the clinical course of cancer in patient cohorts to estimate cancer costs and develop sound methodology to evaluate different treatment and screening regimens.

During the last decades, several models have been developed with an emphasis on describing and modeling the pre-clinical course of cancer (3-8). A workshop among leading academic teams concluded that there was considerable variation in cost estimates used in the various models and that future research should address modeling costs both more precisely and transparently (9). This limitation was also confirmed in a review of economic evaluations of laparoscopic surgery (10).

Compared to estimating the cost of CRC treatment empirically, model-based estimates have several advantages (11-14). Within a model framework, it is easier to adjust for changes like mortality rates, recurrence rates and new treatments. Further, a model facilitates extrapolations of both costs and outcomes, allowing predictions 10-30 years into the future.

The model presented in this paper has similarities to the model of Tilson et al. (15) but with some extensions. Firstly, time is defined explicitly by using a Markov framework instead of decision trees. A three-dimensional data matrix captures time dependence according to the age of the patient and how long he/she has remained in a defined health state. Several other extensions were included in relation to independent costs according to exclusively local recurrence, distant recurrence only or a combination of local and distant recurrence; survival and cost of treatment for re-recurrence, which is defined as a new recurrence after an apparently curative treatment of the first recurrence; a separate decision tree for palliative chemotherapy; side effects from surgery and (neo) adjuvant and palliative therapy.

To improve confidence in models, attention has been paid to transparency and validation (16-18).

The purpose of this paper was to contribute to modeling the CRC cost and survival by presenting a transparent model and validating it. The structure of the Markov model was specified in detail, explaining how different data sources were used to estimate costs and transition probabilities. We validated the model according to standard methods in order to show the precision of the model (18).

The model was intended to be "multi-applicational" (general) to enable the addressing of a range of problems related to CRC treatment (surgery, chemotherapy, radiation, screening, lifestyle changes, etc) and transferable to other countries that have access to a similar type of data.

2 The Model

2.1 The model structure and flow of CRC patients

The main outcomes of the model were recurrence, survival and costs of CRC, which were estimated by means of a semi-Markov model (16-18)(19, 20). The model structure was based on literature about CRC treatment and the natural history of CRC, national guidelines on CRC treatment and expert opinion (oncologist, colorectal surgeon, and a gastro physician). Figure 1 illustrates the Markov model with mutually exclusive health states (squares) and how patients could move between the health states. The model simulates the flow of a 70-year-old cohort of CRC patients from the year of diagnosis through periods of treatment and health states without CRC symptoms, until they died from CRC or other causes or were 100 years old (red lines). The length of one cycle was defined as one year. Each arrow was represented by a transition probability. Loop arrows illustrate health states where the patient can stay for more than one year.

(Figure 1)

The TNM classification system was used to classify the disease stage at the time of diagnosis, where disease is classified in stage I-IV (see definition in Appendix 1).

In the model standard half-cycle corrections were applied to adjust mortality (21, 22). For costs, half-cycle corrections were not explicitly modelled, but done indirectly, as the empirical data used to estimate CRC treatment costs consider compliance and mortality.

2.2 Algorithms and modeling of treatment and disease course

2.2.1 Primary treatment

The cohort entered the model in one of the TNM stages of year 0 when diagnostic and supplementary examinations were performed to establish disease stage, co-morbidity and the patient's general condition. Based on this work-up, it was decided whether the treatment intention was curative or palliative. Curative treatment always implied resection of the primary tumor and regional lymph nodes, with or without pre- or postoperative (radio-) chemotherapy. After the histopathological report was finished, TNM-staging and R- (Residual tumor) classification was made. The treatment was defined as curative (called R0-resection) if the entire tumor was resected, there was no microscopic invasion of the resection margins, and there was no radiological evidence of residual tumor in other organs (no distant metastasis).

In the model, according to the primary treatment (year 0), the patients could go to "*Disease Free"* (DF) after a R0-resection or receive palliative treatment (or no treatment) if curative treatment was not possible. Palliative treatment included R1-2 resections and other palliative surgical procedures and/or (radio) chemotherapy. Subsequently, the patients could die within 30 days after the operation (often due to treatment complications which resulted in the classification of CRC death), die later of CRC or causes other than CRC, or develop a recurrence for which some would receive treatment. A proportion of the patients started palliative chemotherapy during primary treatment and moved to further palliative chemotherapy the following years (years 2, 3 and 4 in palliation).

2.2.2 Follow-up and treatment of recurrence

From year one to four in the "*disease free*" state after primary resection, the patients entered follow-up programs that varied according to the estimated risk of relapse and the national guidelines. From the point of "*disease free",* the patient could either move to the next year in the "*disease free*" state, die (of CRC or other causes) or have a recurrence, *local recurrence* (LR), metastasis (*distant recurrence, DR*) or a combination of the two (*local and distant recurrence, LDR*).

The model principles behind the recurrence stages were similar to the treatment pattern based on the primary diagnosis. The patient would stay in the recurrence state for one cycle and receive treatment independent of whether the intention was curative or not. In the following cycle, the patient either moved to *"disease free"* after LR, DR or LDR, died (of CRC or other causes), or moved on to palliative treatment. It was assumed that after a diagnosis of recurrence, the course of the individual patient would be identical to all other individuals with the same type of recurrence and independent of the TNM stage at the time of primary diagnosis.

2.3 Survival and mortality

In the model, mortality was dichotomized according to cause of death - mortality caused by CRC (disease-specific mortality) or any other cause (all-cause mortality exclusive of CRC mortality). Patients might die after surgery (less than 30 days); during palliative treatment followed by a terminal phase, whether due to CRC or the palliative treatment; or from an unrelated cause in any of the health states defined, including a "*disease free*" state. Dying from CRC within the "disease free" state is a correction for the patients who die from CRC within a month after diagnosis or for cases where the CRC is detected after the time of death (autopsy). Therefore, no CRC treatment costs created by recurrence are included for these patients. This correction comprises from 0.07% (stage I) to 0.7% (stage IV) of the patients every year.

2.4 Tunnel states

Probabilities for recurrence and death often depend on the duration of clinical disease, i.e. the time from diagnosis. This time dependency (memory) was captured in the model by using "tunnel states" (19, 20). By using tunnels, we can incorporate heterogeneity and simultaneously estimate survival and costs according to age groups. Including age is important when evaluating interventions like screening or primary prevention where the individual can be diagnosed with cancer and enter the model at any age.

All the "*disease free"* after primary resection (light blue – Fig. 1), *"disease free"* after recurrence and the three "*palliative*" states were parts of tunnels. The *"disease free"* tunnels begin in year one after primary treatment and are continuous throughout year ten (cycle 11).

2.5 The perspective and cost

The model has the perspective of the health care payer. The CRC treatment costs included in-hospital CRC treatment, including diagnostics, treatment for complications, treatment of recurrence, radiation and chemotherapies, follow-up and patient visits to a general practitioner.

To estimate the cost in each health state, sub-models were used to reflect the treatment pathways. The unit cost of the different treatments was mainly based on the reimbursement systems in Norway. The Hospitals in Norway were reimbursed partly by block grants and partly through fees for service. The fee-for-service component was directly linked with Diagnosis-Related-Groups (DRGs).[2] The unit cost for the chemotherapy drug is based on Oncolex[3] estimates.

To determine cost, frequency and compliance of follow-up and surveillance, we applied market prices, data from Kørner et al. and the national guidelines for CRC-treatment (23, 24).

[2] In 2010, approximately 900 DRGs were used to reflect the hospital case mix. One DRG received a value reflecting the average cost of treating one patient. Each DRG received a weight reflecting the intensity of the treatment compared to treating the average patient.
[3] Oncolex is a Norwegian encyclopaedia for oncology health personnel (oncolex.org). You will find background information and updated procedures for treatment of CRC.

For palliative chemotherapy treatment, a decision tree was used to estimate costs according to treatment paths and was then distributed according to the treatment years in the Markov model. For each treatment in the decision tree, a separate cost model was developed, which took into account the cost of the drug, CT-scanning, complications, and the time spent on therapy by the nurse, pharmacist and medical practitioner. The model corrected for non-compliance and discontinuation of chemotherapy.

2.6 Data source

Inputs were based on Norwegian data as far as possible. An important source was an observational study in the period 1993-2010 of 2049 patients diagnosed with CRC at Oslo University Hospital – Aker (referred to as the OUS data) (25, 26). The OUS data included a wide range of variables related to CRC treatment (mostly surgical procedures) and time to recurrence and death.

Information from the National Patient Register (referred to as the NPR data), based on data related to an analysis by Aas (27), was used to quantify some types of treatments from the years 2003 and 2004. The NPR data were collected for two counties in Norway and should be representative for the general population. There have been differences in CRC risk between regions in Norway. Around the year 2000, the relative risk of CRC for inhabitants in these two counties was close to 1.0 compared to the overall national risk.

Other data sources were national life tables, international scientific publications (overall survival of patients receiving palliative chemotherapy, etc.), and expert opinions in parameters considered not to have essential effects on outcome. Data for treatment after recurrence were limited and based on literature and expert opinion.

A Scandinavian prospective-population-based observational study was an important data source concerning palliative chemotherapy (28).

Calibration is normally used as a complement to data sources, but it was concluded that calibration was not needed due to a good fit of the model.

3 Validation of the Model

The model was validated according to face-, internal-, cross- and external validation (29). We concentrated the validation on survival and the cost of colorectal cancer treatment, being the two main outcomes of the model. They are endpoint estimates of numerous intermediate calculations in the model, and therefore indirectly also represent a rough test of the sub-parts of the model.

3.1 Face validity

By face validity, we assess if the results make sense and can be explained at an intuitive level (29). The model structure, including health states, patient flow and the data used, were closely evaluated by medical experts and could therefore easily be recognized. The estimates used for important cost components during the first year of treatment and during palliative treatment, used established assumptions and classification of treatment options and their costs (see Appendix 1).

3.2 Internal validation

Internal validity implies that the mathematical calculations were correct and consistent with the specification of the model (29). Algorithms checked that the row of the data matrices for the annual transition probabilities summed to one and that the number of patients in the Markov model was constant for all cycles.

Validation of the economic model was more complicated. Extensive use of checking calculations was performed to test if the results based on the model were replicable. Approximately 150 one-way sensitivity simulations were run to test whether the model behaved as expected (i.e., according to size, direction and symmetry). No anomalies were found.

3.3 Cross validation

For cross or between-model validation, we compared models (or methods) which were independently developed, but aimed at estimating the same outcomes, to investigate if they achieved similar results.

3.3.1 Overall survival

A ten-year overall survival estimated by the model was compared to statistical estimations (Weibull distribution, STATA) based on the OUS data (Figure 2). Overall survival was used as an endpoint, because it reflected the sum of all moves, was not used directly as an input in the model, and was normally more reliable than the other relevant output measures.

In cross validation, the degree of model- and data *independence* is important. The higher the degree of independence, the more valuable is the validation. Independence is obtained if the models compared use completely different data sources and apply different types of methods. In the cross validation, different methods were used, but the data were partially dependent. In the model, OUS data were used to estimate disease-free survival and time to recurrence after primary treatment (for the patients who underwent R0 resection), while in the statistical analyses, data for all 2,049 patients were used to estimate overall survival. In addition to the use of OUS data mentioned, the literature and expert opinions were used to find the R0-resection rate in patients with recurrent disease and to estimate the survival for patients in palliative treatment. A simplified model (based on a portion of the patients in the OUS data) was then developed to estimate disease-free survival after R0-resection for recurrence and time to re-recurrence.

The curves in Figure 2 indicated that the structure and assumptions of the model correspond well with the Weibull regression. Even without a preceding calibration of the model, the differences in survival between

the two methods of estimation in the fifth year after diagnosis were -0.002, -0.002, 0.014 and -0.004 for stages I, II, III and IV, respectively and in the 10th year -0.001, -0.018, -0.004 and 0.001, respectively. The area between the curves (based on the model and the Weibull estimation) showed the difference in survival between the two methods, and were 0.27, -0.22, 1.62 and -0.04 months, respectively. Over 10 years, the weighted difference was on average 11.5 days (0.38 month) for all stages.

The curves based on the model for stages I, II and III overestimated the survival during the first years. This seemed to be caused by structural elements in the model due to a mortality lag. A "disease free" patient with a recurrence death within 12 months was not defined as dead during that cycle according to the model (except for a small fraction that would die before knowing about the recurrence) but was rather moved to one of the health states of treatment for recurrence. This could also explain why stage I patients have the smallest deviation (lowest recurrence) and stage III the greatest with II in between. We could reduce this problem by shortening the cycles from twelve to six months or even one month.

Furthermore, the model underestimated the survival curve for stage II in the last part of the 10-year period (Figure 2). The reasons seemed partly to be that patients in stage II were relatively more often struck by isolated local recurrence than the average CRC patient, and patients with local recurrence survived for a longer time than patients who experienced DR or LDR, while the model assumed the same survival time for all three types of recurrence.

The good fit between the statistical estimations and the simulation model of the 40 estimates of comparison indicated that the structure seemed to be close to reality and captured the true treatment pathways.

(Figure 2)

From cycle 11, after completing the "disease free" tunnel, it was assumed no recurrence. For this part of the model, the overall mortality was mainly based on data from the Norwegian Life Table. To verify

consistency with natural survival for the Norwegian population, estimated overall survival from the model was validated against the life table for patients aged 70 to 100 years.

As expected, none of the overall survival curves of the four stages cross, none of these cross the overall survival curve based on the National Life Table, and the curves show a gradual change (Figure 3). The data used were partly dependent in this validation, because the life table was also used in the model as part of the background mortality from cycle 11 or when the cohort was 81 years of age (year 11 in Figure 3). Another weakness in this validation was the expected difference between the natural survival of the general population used in the model and the expected background survival for the CRC group. The latter group seemed to have a lifestyle that increased the risk of death apart from CRC(30-33).

(Figure 3)

3.3.2 CRC treatment costs

Comparing our CRC costs with a non-Norwegian study is difficult as a result of often major differences related to time horizon of costs, treatment regimens, unit costs, general health conditions and whether or not the cost of recurrence and palliative treatment was included. In addition, diagnostics, treatment regimens and cost can change significantly over time. Nevertheless, we compared our results with a recent Irish study that thoroughly described the treatment regimen and other important conditions so that we could correct for the differences in the assumptions of the Irish study and our study(15). The study published by Tilson et al. (2011) was a model study (decision trees) based on 4,268 CRC patients (National Cancer Registry Ireland, 2004–2005), local hospitals' databases and protocols, literature and expert clinical opinions. The Irish model was developed independently from ours both with regard to data and structure.

Our model estimated the total lifetime CRC costs to be as follows: for stage IV patients, €61,396; for stage III patients, €49,894; for stage II patients, €33,501; and for stage I patients, €23,386 (average 2011: 1 Euro = 7.79 NOK and 1 Euro = 1.39 USD). When corrected for the exchange rate (8.19%, average 2008-2011) and annual inflation (3.4%, average Irish Consumer Price Index for health 2008–2011, see www.cso.ie),

the costs for stages I, II and III in Ireland were 17.7, 26.7 and 13.8% higher, respectively, than in our model, while stage IV was 30.7% lower. There were some important differences in prices and treatment regimens between the studies.[4] Adjusting for these factors in our model, the cost difference between Tilson et al.'s and our model (Tilson et al.'s model minus our model) was -3.0, -1.3, 3.6 and -1.2% for stages I, II, III and IV, respectively. These four deviations were all within the estimated confidence interval in the study of Tilson et al., which varied between +/- 12 to 29% of the stage cost estimates.

3.4. External validation

External validation compares actual event data with the result from a model simulating the same scenario. For a multi-application model like ours, validation could be general or specific to each application of the model. "*External validation and predictive validation are critical as they most closely correspond to the model's purpose—to help decision makers anticipate what will occur if they take certain actions*"(18).

3.4.1 Relative survival

The first external validation was done by comparing *relative survival* estimated by the model with patients monitored by the Cancer Registry of Norway, which monitors the whole Norwegian population (about five million), while our OUS data were based on a catchment area of about 4.2% of the total population. Further, as the Cancer Registry of Norway organizes the data differently from the OUS data, the two data sources were highly independent.

In Figure 4, the comparison revealed a 3.9% higher relative survival for the model during the first year, and 0.9, 5.6 and 5.6% lower relative survival five, ten and fifteen years after diagnosis. As observed for the cross validation, this external validation showed that the model predictions were too high immediately after diagnosis, rather accurate after five years, and slightly lower at year ten. Fifteen years after diagnosis, the validation indicated that the difference had stabilized between five and six percent.

[4] Tilson et al. assumed higher prices for resections for both the colon and rectum; less use of palliative chemotherapy; less use of adjuvant chemotherapy for stage III; no recurrence for stage I; an cost for recurrence equal to the cost of stage IV; and no category given for "nonsurgical supportive treatment and care" except best supportive care.

The overestimation of survival up to five years after diagnosis can partly be explained by one-year cycles, as argued above. The general picture beyond five years was a higher mortality in our model. One possible explanation might be that our statistical analyses were based on older data (1993- 2010), while the analyses from the Cancer Registry of Norway displayed relative survival estimates for the follow-up period 2008-10. According to the Cancer Registry of Norway, relative survival has increased gradually during the last decades.

(Figure 4)

3.4.2 CRC treatment costs

In an external validation with a relevant population, *total costs* were compared to empirically estimated ("model-free") total costs based on a Norwegian population study by Aas (27). The methods used for estimation in the two studies were therefore highly independent, although for 16% of the treatments, the two studies used the same data source (NPR data), but these data were collected from different time periods.

Adjusted for the annual price change of the Norwegian DRG's, the estimated CRC costs in Aas were €29,890 for all patients (2011 Euro) in the control group with no screening, while the model estimate was €41,548 (39.0% higher). This difference could partly be explained by the increased intensity of palliative treatment in the period between Aas' study (1999-2001) and our study (2010-2011). In 1999-2001, biological agents were rarely used in Norway. In addition, the use of radiation therapy and surgery for metastases was not included in Aas' study. When adjusting for these two, as well, the model result was 9.1 percent higher than the estimate by Aas. Furthermore, taking into account Aas' study's estimated costs for a five-year period, the model estimate was 3.1% higher than Aas' model-free estimate. Additionally, corrections due to different follow-up schemes for the two periods must be done. Our model was based on the Norwegian guidelines from 2010, while Aas' study was based on the actual follow-up years 1999-2001(24). If we instead use the guidelines from that period, the model estimate for the average CRC cost was 1.3% higher than the model-free estimate (34). Both with and without this last correction, the model

seems to fit well when taking into account that the lower and upper confidence interval for Aas' CRC cost estimate was 11-12%.

4 Discussion, Application and Further Improvements

This study demonstrates a multi-applicational (general) model for estimating survival and costs for CRC patients. The validation of the model revealed a good match with reality both in survival and costs. The model is suitable for addressing a wide range of CRC-related themes, most importantly the estimation of cost and survival associated with different treatments and prevention measures. Such information is essential for future revisions of guidelines and health care providers.

4.1 Application of the model

The following applications and advantages of the model should be emphasized. The model (i) estimates the costs and survival time of an average CRC patient according to different disease stages; (ii) estimates final outcomes from changes in intermediate outcomes such as decline in both recurrence and mortality rate due to improvement in preoperative diagnostics; (iii) can be used in economic evaluations by applying modest adjustments and developments needed to perform economic evaluations of different types of screening, prevention, introduction of new treatment and follow-up alternatives; (iv) estimates resource use; (v) can adjust for changed parameters over time (time-dependency) and simultaneously account for the time since CRC treatment, consequences of CRC patient age, alterations in treatment, and changes in cost and resource-use over time (i.e., by using the eight tunnels and the three-dimensional data matrix); and (vi) is transferable to other countries with access to the same types of data. Since calibration has not been used in this model, applying data from another country and building the model with the

recommendations and assumptions provided in the present article and appendix should, in principle, effect a similar goodness of fit. See more on applications in Appendix 2.

4.2 Weaknesses and further developments of the model

The cycles in the model were set to one year, which to some extent restricts the preciseness of the model. Linearity is especially likely to be an unsatisfying approximation during the first year after a diagnosis of stage IV, the first year after a diagnosis of recurrence, and the first year of palliative treatment. The problem would be reduced if the cycles were reduced. One-month cycles could be incorporated into the model by changing the cycles' lengths for all health states or by building separate sub-Markov models for selected health states, making the cycle length shorter (such as a cycle length of a week or a month) for the selected states and retaining the one-year cycle for the other health states. Shorter cycles would make the model more complex and would require more detailed data, which accentuates the trade-off between model complexity and accuracy. Our plan for the next generation of this model is to include shorter cycles for some health states.

The OUS data range from 1993-2010. Since some of these data are relatively old, survival in the model is lower, which can be explained by the older and less effective treatments. The size of these deviations are 0.9%, 5.6% and 5.6% lower relative survival at five, ten and fifteen years, respectively, after diagnosis when the model estimates are compared with data from the Cancer Registry of Norway (see Chapter 3.4.1).

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

stages. These differences are quite small and could only to some extent affect the external validation between the model and data from the Cancer Registry of Norway.

The palliative submodel was suitable for exploring treatment paths and costs, but there was no explicit, built-in time dimension. An approximation was therefore used to disperse the costs over time. A better solution could be to build a separate sub-Markov model with weekly or monthly cycles for palliation into the main model.

The model has 70 health states, eight "tunnels," and uses a three-dimensional data matrix to handle the changing rates of recurrence and mortality by age and year since primary CRC or recurrence. The complexity could be a drawback for decision makers to fully understand all the mechanisms of the model. Still, hardly any part of the model could be further simplified; quite the contrary seems to be the issue.

In the model, the OUS data was used as the basis for the survival analysis. As the OUS data was collected over a long time period, it could imply that subgroups of patients are treated differently from current guidelines. Basing the inputs on newer data could adjust for these differences.

Many articles analyze the costs during the last year that patients are alive or for other time periods, but no relevant articles analyzing costs of the activity related to "best supportive care" were found. We assume, however, that this cost is partly included in "digestive malignancy" (Table 7, Appendix 1).

There seems to be a lack of data on the resource use related to treatment for local and distant recurrence, separately or combined, mainly because the relevant registers are not organized to estimate this. Solutions could be to do observational or retrospective studies on resource use after a recurrence or expand the registries to include such data.

In such general models as ours, external validations can be applied to some components of the model or to the model as a whole(18). Our external validation was applied to the model as a whole by validating for

the main outcomes: survival and cost. One problem with these could be that errors in different parts of the model may cancel out each other and in sum give a result for the model consistent with the external data. ~~In~~ Future validations of the model should therefore also focus on different components of the model. Some of these could be certain categories of cost (e.g., palliative chemotherapy and treatment for metastasis), time to recurrence and time to re-recurrence.

Our validations for survival were comparisons with observed data for survival rates at whole-year points. For future validations of the model, a suitable alternative to this approach could be life years or life expectancy.

Further development of the model should include quality of life and elaborate on the palliative and re-recurrence part of the model. Including quality of life during primary treatment, treatment for recurrence and during palliative care would, to a greater extent, capture the severity according to the TNM stage. The effect of colorectal cancer diagnosis on quality of life in the "disease-free" stages should also be considered.

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Figures legends:

Figure 1. The structure of the semi-Markov model.

Figure 2. "Model" means the overall survival curve simulated by the model, and "Weibull" means the overall survival curve estimated with Weibull distribution using our data from Oslo University Hospital.

Figure 3. Overall survival for the Norwegian population (without CRC) and for CRC patients according to the disease stage.

Figure 4. External validation between the model and data from the Cancer Registry of Norway.

Figures:

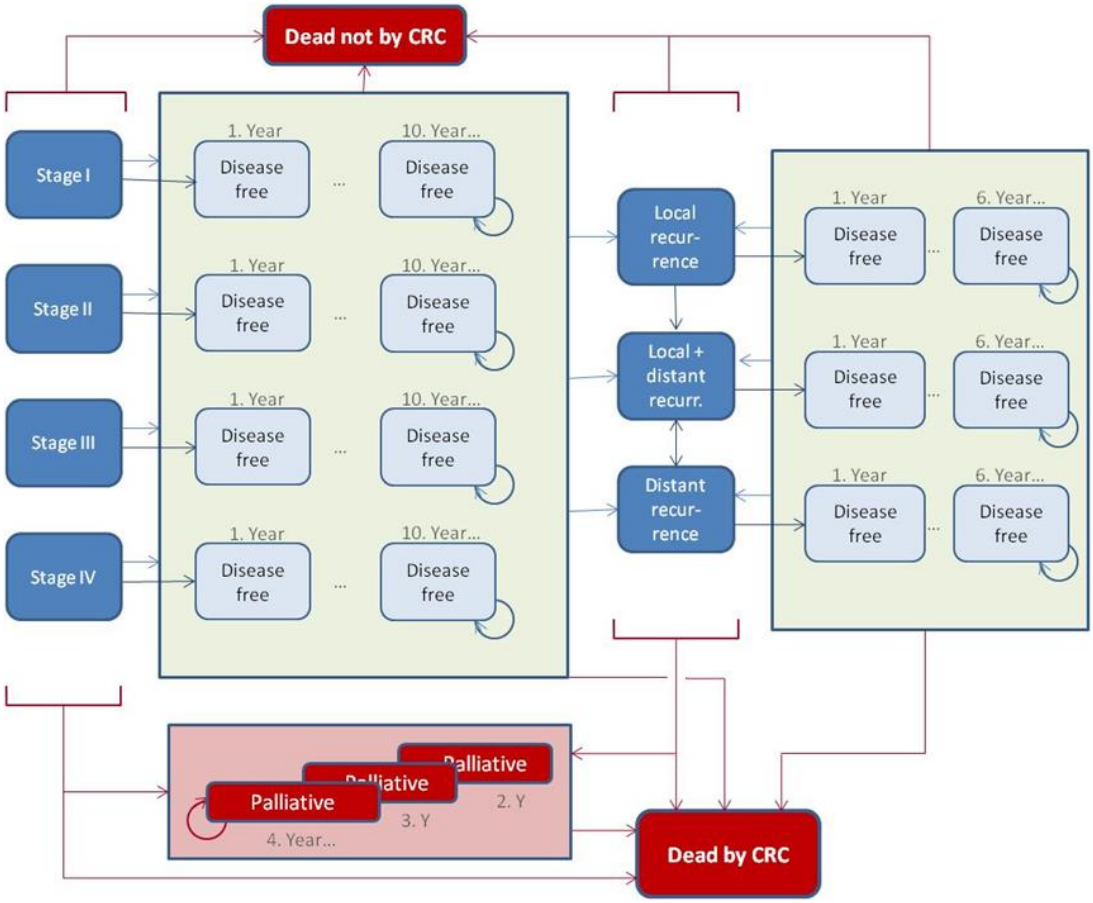
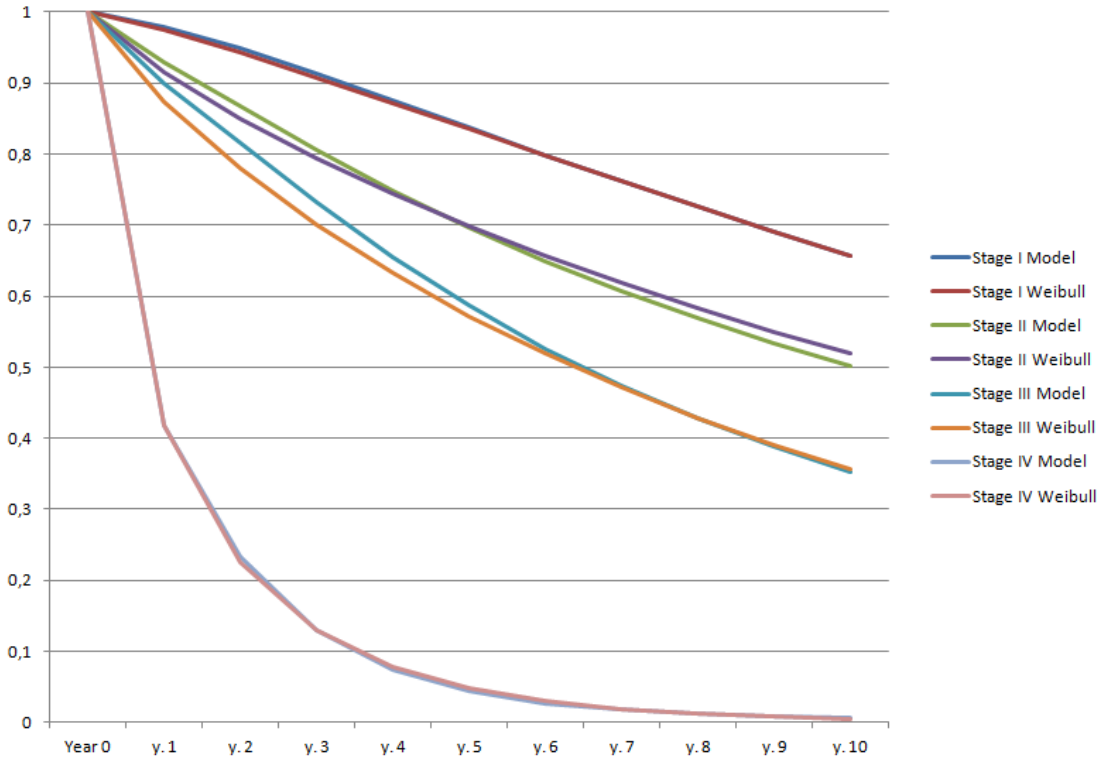


Figure 1


1
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Year 0
y. 1
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y. 3
y. 4
y. 5
y. 6
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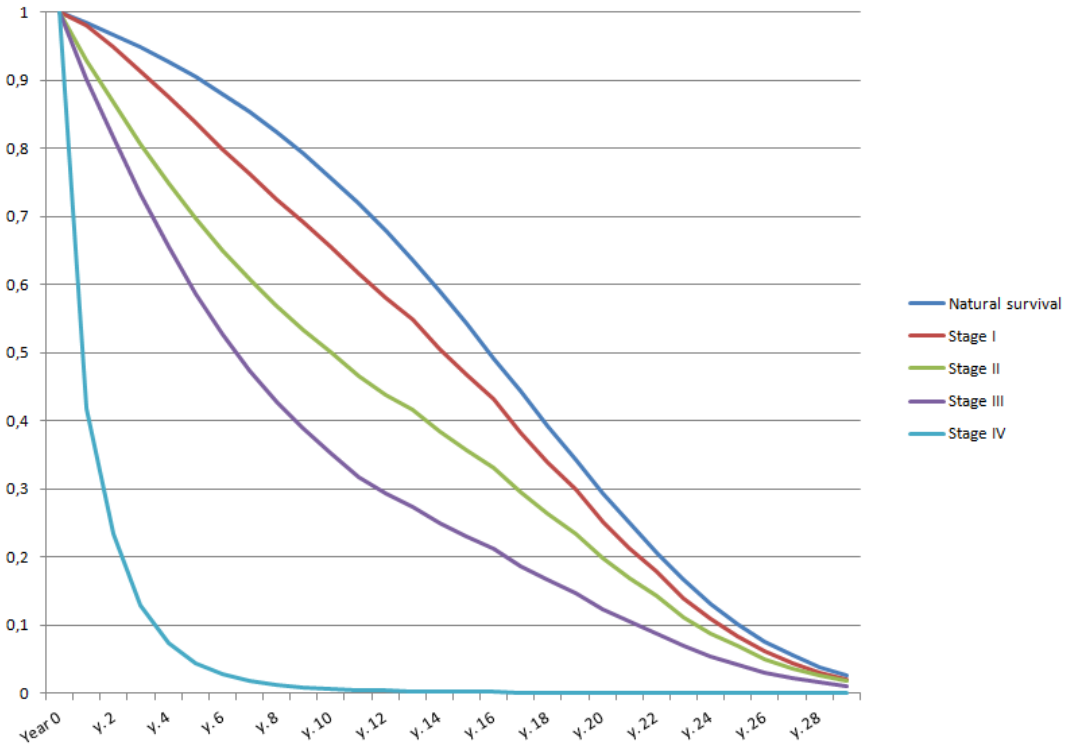
y. 8
y. 9
y. 10
Stage I Model
Stage I Weibull
Stage II Model
Stage II Weibull
Stage III Model
Stage III Weibull
Stage IV Model
Stage IV Weibull

Figure 2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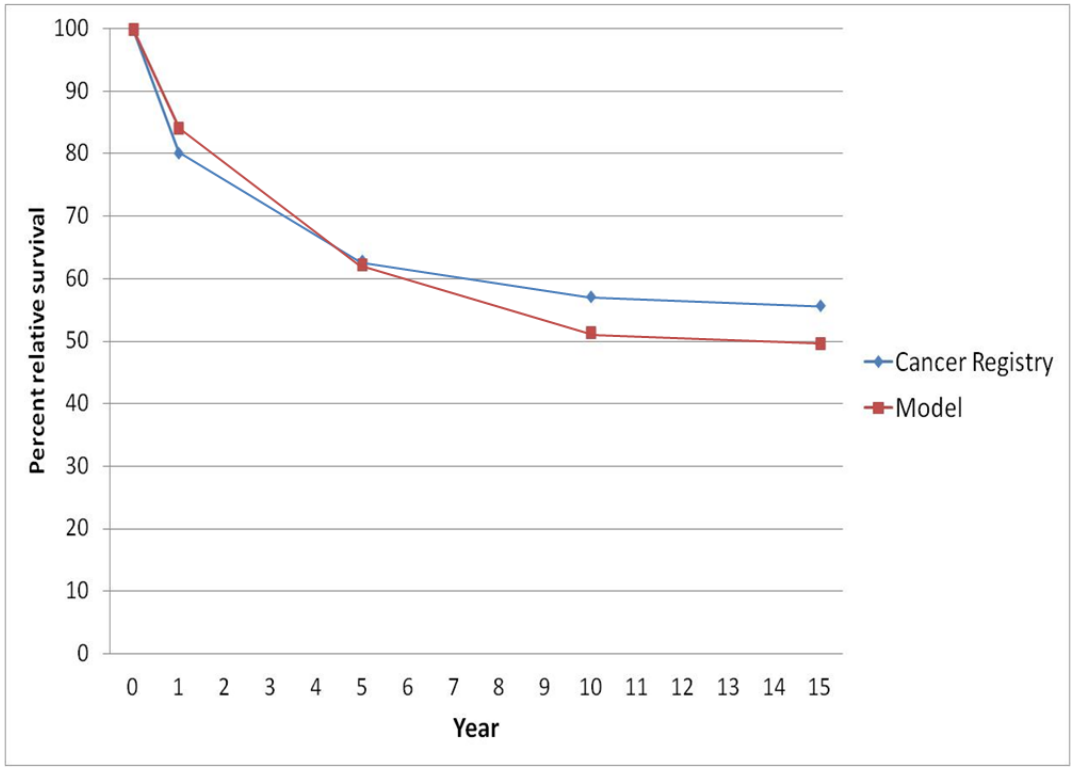
y. 26
y. 28
Natural survival
Stage I
Stage II
Stage III
Stage IV

Figure 3.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Percent relative survival
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Year
Cancer Registry
Model

Figure 4.

Appendix 1:

(App. 1: Published in a Web-only format)

Data and statistical analyses

1. Data source

In this study, as far as possible, inputs were based on Norwegian data. An important source of input data was an observational study at Oslo University Hospital – Aker (OUS), in the following referred to as OUS data, which included a wide range of variables related to CRC treatment. Most of the variables described different surgical procedures, the times to recurrence and the time of death. The study consisted of 2,049 patients diagnosed with CRC in the period 1993-2010, including all the CRC patients diagnosed at OUS. The hospital treated all patients from a defined catchment area of approximately 210,000 inhabitants.

(Textbox 1)

The TNM classification system (AJCC/UICC) was used to classify the disease stage at the time of diagnosis, where T-stage reflects the depth of tumor invasion into and through the bowel wall, N-stage reveals whether or not there are metastases in the regional lymph nodes, and M-stage shows the presence of distant metastases. According to TNM, the disease is classified in stages I-IV. Stage I means the tumor is confined to the intestinal wall; stage II means the tumor is invading through the intestinal wall (and might invade adjacent organs or perforate the visceral peritoneum); stage III has lymph node(s) metastases; stage IV has distant metastases.

Information from the National Patient Register (in the following, referred to as the NPR data), based on data related to an analysis by Aas (27) was used to quantify some types of treatment from the years 2003 and 2004. The data were collected for two counties in Norway and should be representative for the general population.

National life tables (Statistics Norway) and four international published papers estimating the overall survival for patients receiving palliative chemotherapy, were used. Two of the studies were based on European populations (35, 36), one on North Americans (37), and the last on Scandinavian countries (38).

When information from public sources was not available, *expert opinion* (oncologist, colorectal surgeon, and a gastro physician) was considered a legitimate method for assessing parameters (29). Generally, expert opinions were used if the parameters were considered (based on literature, model simulation or expert opinion) not to have essential effects on output. If they were considered to affect the output significantly, sensitivity analyses were carried out. Expert opinion has been used in computing parts of the treatment model for palliative chemotherapy, partly for the use of radiation and for certain parts of the sub-model for recurrence and re-recurrences.

Calibration is normally used as a complement to data sources (39). Calibration would imply a systematic adjustment of model parameters by letting the model output govern the model input. After comparing the result of the model with the data from the same population (see Chapter 4), it was concluded that calibration was not needed due to a good fit of the model.

Input data presented here are mostly estimates from calculations and statistical analysis, and presented with a precision that does not always correspond with the quality of the underlying data source. This high "precision" is used in this appendix to make it easier for the readers to test the model by doing their own simulations with in-data close to the data calculated in our Excel-based model.

Endpoints have often been defined differently in studies of CRC, leading to a lack of comparability, so our CRC survival analyses were performed with endpoint definitions agreed upon in a recent consensus conference (40) and shown in Table 1.

(Table 1)

2. Incorporation of data

Important factors in the model, such as survival curves, transition probabilities and frequencies were derived from data in the literature, from the primary CRC data or from official registers.

Some of the data could directly be found in published papers, such as the probability of a patient getting a certain treatment, e.g., the probability of prescribing adjuvant chemotherapy to a patient with a stage-III disease. Often, available data could not be directly incorporated into the model.

Important sources of data for modeling the course of CRC were different kinds of survival curves presented in literature.

These often presented the cumulative survival for a certain period and indicated the probability for an average patient to survive at least to time t. given by

$$S(t) = P(T > t) = 1- F(t)$$

where *t* was years and F(t) the cumulative density function. Let S (t-u) be the cumulative survival for the last period in time, where the *u* is the length of a Markov cycle. Then the probability of surviving through one cycle was defined as

$$s(t) = S(t) / S(t-u). \qquad (0)$$

Based on Equation (0), the probability of failure (recurrence or death) during a cycle was defined by

$$tp(t_u) = 1- s(t) = 1 - [S(t) / S(t-u)]. \qquad (1)$$

If two- and three-year survival was 0.9 and 0.8, respectively, then the probability of staying alive from year two to three was S(3) / S(3-1) = 0.8/0.9 = 0.89, and the transition probability of dying between years two and three would be 1 – [S(t)/S(t-u)] = 1- (0.8/0.9) = 0.11.

Based on data from four studies (35-38), Equation (1) was used to estimate the survival function for patients going through palliative treatment. The survival curves from each study were scanned and visually extracted. The four datasets were merged by weighting each study equally, and the probability of surviving years one through four were computed to be 0.675, 0.350, 0.175 and 0.087, respectively. Finally, equation

(0) was used to estimate the transition probabilities $tp_{1,a}^{Pa,Pa}$ (see textbox 1) of staying alive between each cycle (or year), such as between year one and year two.

2.1 Estimating survival curves and transition probabilities based on individual data

Several statistical models can be applied to estimate the transition probabilities from our individual level data. As pointed out in Briggs et al. (19), the parametric survival function, Weibull, is preferable, as it allows the transition probabilities to change as a function of duration (such as time since diagnosis). Based on the Weibull model, separate hazard rates and transition probabilities could be estimated according to TNM stages for each year. The following equation and parameter was used:

Let $S(t) = \exp[-H(t)]$ and $H(t) = \lambda t^p$, and inserted in Equation (1) the probability of failure during one cycle was given by

$$tp(t_u)_{fail} = 1 - \exp[\lambda(t-u)^p - \lambda t^p] \qquad (1^*)$$

where λ was the "scale" factor and p the "shape" factor. If p<1, then (and statistical significant) there was evidence for a decreasing hazard over time. Further, let $\lambda = \exp(a_0 + \sum a_i X_i)$ were *i* goes from 1 to *n*, then the nomenclature was given by

$$tp(t_u)_{fail} = 1 - \exp\mathbf{(}[\exp(a_0 + \sum a_i X_i)](t-u)^p - [\exp(a_0 + \sum a_i X_i)]\, t^p\mathbf{)} \qquad (2)$$

where a_0 is the constant, a_1 referred to age at diagnosis and a_2 to gender. The estimated coefficients are reported in Table 2. Based on Equation (2), the transition probability of no failure during one cycle was given by

$$tp(t_u)_{no\text{-}fail} = 1 - tp(t_u)_{fail} = tp_{t,a}^{TNM,TNM} \qquad (3)$$

The estimated coefficients from Equation (2) were used to estimate the transition probability of a failure during one specific year conditioned on surviving until the start of that specific year, reported in Table 2. For instance, will the transition probability for a cohort of 70-year-old individuals, diagnosed with TNM, stage II and with a 50/50 mix of men and women be 0.0757. Thus, according to Equation (3), the transition probability $tp_{2,72}^{IIc,IIc}$ of staying in *"disease free after II"* from year two to three would be 0.9253 (1-0.0757).

$$tp(3_u)_{fail} = 1 - \exp([\exp(-6.91471 + 0.0389469 * 70 + 0.266219 * 0.5)](36-12)^{0.7850102}$$
$$- [\exp(-6.91471 + 0.0389469 * 70 + 0.266219 * 0.5)] * 36^{0.7850102})$$

= 0.0757

where the parameter *u* (length of Markov cycle) was set to 12, because months were used in the analysis, while the length of a cycle was measured in years. Thus, after being treated according to the R0 resection and surviving without recurrence during the first and second year, 0.0757 of the patients would get a recurrence (local, distant, or both local and distant recurrence) or die of causes other than CRC during the third year. Then, according to Equation (3), the transition probability $tp_{2,72}^{IIc,IIc}$ of staying in *"disease free after II"* from year two to three would be 1 – 0.0757 = 0.9253.

(Table 2)

To estimate the transition probabilities from the primary year of treatment (year 0) to *"disease free after TNM,"* the above method needed to be adjusted. Only a proportion of the patients received R0 surgery, e.g., 0.943 in stage III (Table 4). Thus, if 0.824 of the R0 patients were estimated to be eligible for the "*disease free after TNM*" state (disease free survival) after primary treatment, then 0.824 * 0.943 = 0.777 of all the patients diagnosed with stage III would move from the clinical stage III to the first year of "disease free after stage III", defined by $tp_{0,70}^{III,IIIc}$. The R0 correction was particularly important for stage IV, where only 0.059 got a R0 operation. In Table 3, row four, all the adjusted transition probabilities were reported. Adjustments were also needed for the transition probabilities connecting the treatment year after recurrence and the first year of being "*disease free after recurrence*". For the rest of the years of "*disease free after TNM*", Equation (3) was used to estimate the transition probabilities directly from the Weibull regressions, as argued above.

(Table 3)

Transition probabilities from primary treatment to *recurrence* were more complex to estimate. First, the parameters for time to recurrence (TTR) were estimated using the OUS data similarly to disease-free survival (DFS), and then the transition probabilities for recurrence were estimated by using Equation (2), i.e., the proportion of CRC-patients suffering a recurrence during primary treatment (year 0). The

transition probability from primary treatment to recurrence also had to be adjusted by categorizing recurrences into local recurrence, distant recurrence and both local and distant recurrence.

The estimated transition probability from primary treatment in clinical stage II to local recurrence for a patient 70 years old was, as an example, defined by

$$tp_{0,70}^{II,LR} = REC_{II} * R0_{II} * LR\textit{of}R_{II} * (1 - CD_{REC30d} - CD_{TNM+REC}) \quad (4)$$

where $R0_{II}$ was the portion of the stage II patients having R0 surgery and categorized as disease-free (Table 4) - only a disease-free person could get a recurrence. REC_{II} was the probability of getting a recurrence during the first year of primary treatment for a stage-II patient, given that the patient had R0 surgery for the primary CRC. Further, $LR\textit{of}R_{II}$ was the portion of the REC_{II} getting a local recurrence (LR). CD_{REC30d} was the probability of dying during the first month after recurrence and was estimated to be 0.0422. These patients were excluded, because it was assumed that they died within 30 days after diagnosis of recurrence, or the recurrence was diagnosed post-mortem (autopsy). Further, it was assumed that these patients did not receive any treatment. $CD_{TNM+REC}$ was the probability of dying from CRC in the period of 2-12 months after the primary treatment, given that the patient had a recurrence that year. Hence, a double-counting of cost for patients dying within the first year was avoided (for both primary treatment and the treatment cost of recurrence). Inserting the coefficients from Table 4 for a 70-year-old patient in Equation (4), the transition probability was

(Table 4)

$$tp_{0,70}^{II,LR} = 0.0994 * 0.957 * 0.151 * (1-0.0422-0.107) = 0.0122$$

To estimate the transition probabilities for the subsequent years of recurrence from the health state of, e.g., "disease free after II" (see Figure 1), another formula was applied. For instance, the transition probability of a local recurrence (LR) for a stage-II patient in year three in the "disease free after II" was given by

$$tp_{3}^{IIc,LR} = (REC_{II,3} - (REC_{II,3} * CD_{REC30d})) * LRofR_{II} \quad (5)$$

$REC_{II,3}$ was the probability of a patient getting a recurrence in stage II, given R0 surgery for the primary CRC and no recurrence until the end of the third year. By estimating $REC_{II,3} * CD_{REC30d}$, the probability for the stage II patients with recurrence to die within 30 days was found. $REC_{II,3}$ was estimated by Equation (2) to be 0.04635. Inserting this result together with the parameters in Table 4 in Equation (5), the transition probability used in the model for stage-II patients moving from "*Disease free after II*" in year three to treatment of local recurrence during year four was given by

$$tp_3^{IIc,LR} = (0.04365 - (0.04365 * 0.0422)) * 0.151 = 0.00631$$

To estimate survival after recurrence, some simplifications were carried out because of the scarcity of data. Overall survival after recurrence (Table 2) was estimated, but due to lack of data, estimating re-recurrence and disease-free survival was impossible. As an approximation, time to recurrence and disease-free survival for Stage IV was used (Table 2) and adjusted by the difference between overall survival for recurrence and Stage IV.

(Table 5)

The adjusted time to recurrence and disease-free survival was shown in Table 6.

When considering the changes in both disease-free survival and time to recurrence and re-recurrence in the states *"disease-free after TNM" and "disease-free after REC"*, tunnels of ten and six years were built respectively. An essential part of building the model was to use precise clinical endpoints, and the definitions of events (failures) and censoring of data were defined in Table 1. A 10-year time frame was chosen for the tunnel states after primary treatment; consequently, no recurrence was assumed to occur 11 years after diagnosis (year of primary treatment and 10 years into *"disease free after TNM"*). Further, time in the tunnel *"disease free after REC"* was limited to six years, as only a small fraction was left in the tunnel and the re-recurrence rate seemed to stabilize.

(Table 6)

2.2 Mortality

2.2.1 CRC death

CRC-death means death caused by colorectal cancer disease and death caused by CRC treatment. In the model, CRC deaths mainly occur in the year of treatment for primary diagnosed CRC or for recurrence and during the year with palliation. This means, if a patient got a recurrence in month four in year three after the primary treatment and died six months after CRC, then the model defines this as a recurrence, and the patient would move to the recurrence state for the next year, receive treatment, and die in that state of health (except those who die within 30 days after recurrence, as mentioned in the chapter above). The effect of this simplification is discussed in the article.

To estimate the overall survival curve for the patient receiving palliative chemotherapy, the average of four studies was used (35-38). The percentages of patients surviving the first four years were 0.675, 0.350, 0.175, and 0.087, respectively. Equation (1) was used to estimate the transition probability of staying alive. To estimate the transition probabilities from the primary treatment of recurrence (first year of palliative treatment) to the second year of palliative treatment, we used Kaplan-Meier on OUS data and estimated the overall survival for the three groups of recurrence patients. The parameters used for mortality the first year after recurrence are 0.211, 0.593 and 0.427 for patients with local (LR), local and distant (LDR) and distant recurrences (DR), respectively.

Based on OUS data, the probability of dying of CRC during the primary treatment year (according to stage) was estimated to be 0.0045, 0.0418, 0.0560 and 0.5305 for stage I, II, III and IV, respectively.

2.2.2 Non-CRC mortality

In the model, a distinction was made between mortality caused by CRC and all-cause mortality other than CRC. For the first 10 years after primary CRC-treatment, for a patient considered to be disease-free, the non-CRC mortality rate was calculated based on the OUS data according to stages I, II and III. The calculated mortality rate for the first years after primary CRC treatment was higher for 70-year-old patients considered to be disease-free than for cohorts of the same age in Norway. This could be attributable to

the side effects of the treatment or co-morbidity by other lifestyle-related diseases than CRC. At the end of the 10-year period, however, the mortality was 1.7 – 2.4% less for stages I-III than the normal rate, which could be attributed to a situation where the frailest persons died at the beginning of the period. After the 10-year period, this difference was subtracted from the relevant age-specific mortality rate collected from the Norwegian Life Table, and the result was used as non-CRC mortality for patients of ages 81-99. This age span was split into the age groups 81-83, 84-86, 87-89, 90-92, 93-95, 96-97 and 98-99. For stage IV, the non-CRC mortality was estimated to be higher than the normal population in the whole 10-year period. As an example, the non-CRC mortality for a patient of 70 years at the time of diagnosis who entered stage II and was disease-free for three years was given by

$$tp_{3,73}^{IIc,D} = 1 - tp_{3,73}^{IIc,REC} - tp_{3,73}^{IIc,IIc} - tp_{3,73}^{IIc,CD}$$

Where $tp_{3,73}^{IIc,CD} = REC_{II,3} * CD_{REC30d}$

The same approach was used to estimate the non-CRC mortality for those disease-free after recurrence, except that the tunnel-state period lasted for six years. The same mortality probability was then used for all three types of recurrence (Table 6).

The yearly probability of non-CRC death for patients in palliative chemotherapy treatment was assumed to be 4.66% the first 10 years and thereafter followed the same change in mortality risk as for those disease-free.

2.3 The data for the economic models

Major cost components in this model were diagnostics; primary treatment (the first year after diagnosis), including surgery, chemotherapy, radiotherapy and side-effect treatment; follow-up; treatment related to recurrence (first year after recurrence); and palliative treatment.

The health care cost per person per cycle depended on health states. By multiplying the cost for one patient staying one year in a health state by the number of patients staying in that specific health state for the same year, the total cost for all patients in each health state per year was estimated. The expected total

CRC cost per patient was estimated by aggregating the cost over the total lifespans of the patients for all health states.

Discussions about treatment often concern colon or rectum cancer, not colorectal cancer. The model merges these two together. To analyze colon and rectum cancer separately, the present model structure could be used for both, but different data for treatment cost, type of treatment and recurrence rate have to be applied.

2.3.1 Diagnostics

When colorectal cancer is suspected, investigations to confirm the diagnosis and staging of the disease are carried out. The costs related to these examinations are listed in Table 8. In the model, every patient was assumed to receive one unit of each type of examination, except for rectal ultrasound and MRI, which was only received by patients with rectal cancer.

2.3.2 Primary treatment cost

In the model, the first year of treatment included cost of preoperative examinations, cancer treatment, palliative treatment of patients with non-resectable synchronous metastatic disease and the initial part of the follow-up. The quantity per patient and the cost per unit for the different components in the treatment are listed in Table 7.

Generally, several of the frequencies were estimated by using a decision tree, where the distribution of CRC diagnosis between colon and rectum cancer was an important parameter. Based on OUS data, the percentage diagnosed with colon cancer at stages I, II, III and IV were 51.0, 68.1, 65.9 and 70.6, respectively.

The probability for a patient in stage II of receiving "colon resection with no complications (DRG 149)" was 0.401, while it was 0.023 for a patient in stage IV. The major treatment category for a patient diagnosed with a stage IV was "digestive malignancy with complications", DRG 172,(27) where the proportion of patients that received such treatment during the first year after diagnosis was 1.525 – i.e.,

patients in this category had more than 50% probability of receiving the treatment (DRG 172) more than once in the first year.

The unit cost for DRG rows no. 1-19 (Table 7) was based on DRG weights, while the unit cost for no. 20 and 21 was estimated on the basis of drug cost, time use, CT-scanning, and side effects.

The source of the frequency estimate for stages I-IV, rows five to six and eleven to thirteen (Table 7) were based on NPR data (27). The other frequencies in rows 1-14 were based on OUS data.

The parameter for stage IV concerning metastasis (rows 15-18) was based on literature (41, 42), Norwegian guidelines(24) and expert opinions. It was assumed that 0.5 of the stage-IV patients had metastasis in the liver, and 0.25 of these were eligible for resection. The equivalent parameters for metastasis in the lungs were 0.25 and 0.075, respectively. Further, resections for metastasis in any other organs were not included. Rows 17 and 18 indicate no-surgical supportive treatment and care and were adjusted upward to cover the all costs for treatment and care for metastasis.

The frequencies in rows 20 and 21 were based on data from literature and expert opinion (43-48).

2.3.3 Follow-up

After CRC diagnosis and primary treatment, the patients were allocated to regular *follow up,* which could be given during the year of primary treatment (year 0). The frequency for the different types of *follow-up* and the cost per-unit of follow-up for stages II, III and IV were shown in Table 8. For a patient treated for stage I, one unit outpatient consultation, CEA-test and colonoscopy during the primary treatment year after surgery, and one outpatient consultation and CEA-test annually during the ensuing five years was assumed. The follow-up frequency was based on national guidelines (24), and the rate of compliance was based on literature (23).

2.3.4 Recurrence

The data for treatment after recurrence was limited and not included in Table 7, but based on literature, similarities with the primary treatment shown in Table 7 were assumed. For a local recurrence, the frequencies of treatments described in rows one to four (Table 7) were estimated by assuming that 30% of all local recurrence underwent an attempt of curative resection of the recurrent tumor, and this was split between the colon and the rectum, as for stage III. The frequency of treatment related to rows 11-13 was assumed to be identical with stage III. For radiotherapy (row 19), the frequencies were assumed to be 0.215, based on the Norwegian Rectal Cancer Registry and literature (45). For palliative chemotherapy (row 20), adjustments were made, as many patients do not receive palliative chemotherapy due to old age, co-morbidity and poor performance status (28). The first period after local recurrence, the frequency for receiving palliative chemotherapy was in fact marginal, but some period after diagnosis, a proportion of these patients would receive palliative treatment. This proportion was assumed to be 0.49 and was used in the estimation of LR treatment cost.

For distant recurrence (DR), the frequencies were assumed to be identical with stage IV for rows 13 and 15-21. For patients with both local and distant recurrence (LDR), the same parameters as for stage IV were used, except that the following was assumed: there was (i) no major resection, (ii) the probability of getting palliative treatment was increased to 0.754, and (iii) frequencies in rows 19 and 21 were assumed to be zero.

2.3.5 Radiotherapy

To find the parameter for radiotherapy in Table 7, we used decision trees and split the CRC patients into those with colon cancer and those with rectum cancer and used literature and expert opinion to get estimates of radiotherapy use (28, 43, 46-48). Further, for some of the parameters, we also had to consider that only patients with *resection* in stages I–III receive radiotherapy. The cost per fraction of radiotherapy is based on the DRG score, and patients were assumed to have 25 fractions each.

(Table 7)

2.3.6 Adjuvant and perioperative chemotherapy

The parameter for adjuvant chemotherapy stages II and III was estimated the same way as for radiotherapy by dividing colon and rectum cancers. Literature and expert opinion was used to obtain estimates for chemotherapy use (49). For rectum stage II, we assumed no adjuvant chemotherapy, according to Norwegian guidelines (24). A problem with these parameter values is the changes over time. The administration of adjuvant chemotherapy in stage-III patients older than 75 years increased from 19% in the years 1989–1993 to 79% in 2004–2006, and from 1% to 19% in these periods for stage-III patients 75 years or older (43).

Perioperative chemotherapy was only assumed for stage IV, and based on expert opinions, 10% of the stage IV patients are assumed to receive this therapy (50).

For estimating the cost per therapy for stage III in Table 7, row 21, we assume nine rounds of oxaliplatin therapy (development of neurotoxicity) and 12 cycles of 5FU. We also assume that 50% receive 5FU and the other 50% receive the other therapy. For stages II and IV, we assume 12 rounds of therapy for both.

The cost of the drug from pharmacy is based on oncolex.org. Further, we took into account the cost of CT-scanning, complications, and time that the nurse, pharmacist and medical practitioner use when giving the therapy.

(Table 8)

2.3.7 Palliative chemotherapy

The structure of the data for palliative chemotherapy treatment required that a decision tree (Figure 5) be used to estimate costs according to treatment paths before being distributed to the treatment years in the Markov model. In Figure 5, number at each branch indicated the conditional probability, and the number in the brackets was the joint (total) probability for obtaining a certain type of treatment for a patient starting with palliative chemotherapy treatment. As an example, it was assumed that 71% of the patients

have good health (high PS) and obtained first-line palliative chemotherapy treatment. Of these patients, 40% receive bevacizumab, together with FLIRI or FLOX, which constitutes 28.4% (0.71 * 0.4 * 100%) of all patients receiving palliative chemotherapy. Of the others, 30% received FLIRI and 70% FLOX (51). Population-based studies shows that approximately one third of mCRC patients do not receive palliative chemotherapy at all (28, 43, 46-48). In the model, 61% of stage-IV patients received palliative chemotherapy(28, 43, 46-48). Of the patients receiving first-line treatment, 60% received second-line palliative chemotherapy treatment (36). Of these, 60% will be KRAS wild types and suitable for EGFR (epidermal growth factor receptor) inhibitor treatment.

For each treatment in the decision tree, separate cost models took into account the cost of the drug, CT-scanning, complications, and time the nurse, pharmacist and medical practitioner use when giving the therapy. Table 9 shows the cost of components for the different palliative chemotherapy treatments. The medicine costs include all costs at the pharmacy (drug, time use, equipment, etc.) and were derived from oncolex. The cost of 5-FU/FA (5-fluororuracil/folinic acid) was based on the Nordic 5FU/FA schedule (Nordic Flv) (38). The costs related to CT, time usage and treatment intensity were derived from literature (52). Unit costs for side effects (excl. nausea) were derived from the DRG system 2011. The model is corrected for non-compliance and withdrawal from the chemotherapy treatment.

(Figure 5)

The cost model for palliative treatment above has no timeline, which complicated the discounting of the costs. As a simplification, we have distributed the total costs for the three lines of treatment over a three-year period and then summarized the total costs for all three lines. The total palliative treatment costs were €35,880 and were distributed to each treatment year (one, two and three) with the weights of 56.3, 34.9 and 8.9%, respectively.

(Table 9)

Appendix 2:

(App. 2: Published in a Web-only format)

More on application of the model

Some applications and advantages of the model should be emphasized. First, the most obvious and direct use of the model is to estimate the cost and survival time for an average CRC patient according to disease stage. The CRC costs can be divided into different cost components, such as primary treatment, follow-up and palliative treatment. Different survival distributions can be estimated by using different endpoints and can be performed with stratification by stage and R-classification after the primary treatment or after different types of recurrence.

Second, the model can *estimate final outcomes from change*s in intermediate outcomes. The model estimates changes in costs and survival by applying different rates of recurrence or mortality, such as a decline in recurrence and mortality rate due to improvements in preoperative diagnostics, surgery and other treatment modalities for patients treated at a specific hospital. Incremental costs per patient due to marginal changes in resource use can also be estimated, such as an increased use of bevacizumab therapy or increasing unit prices, e.g., the price for drugs. Based on intermediate outcomes from randomized controlled trials - like the percentage of the population diagnosed with CRC; distribution between stages; recurrence or the survival rate after, for instance, three or five years; or relative risk - the model can estimate final outcomes like treatment costs and overall survival during the lifespan until the age of 100 years.

Thirdly, the model can be used in *economic evaluations*. By applying modest adjustments and further developments, the model is suitable for performing economic evaluations of different types of screening

and prevention and follow-up. The model can also evaluate the effects of present or future variations in treatment strategies, including new surgical techniques and technology, an increased and changing use of chemotherapy, the indication of a treatment shift, increased treatment of elderly and the cost of implementing a new drug treatment. The general structure of the model enables comparative analysis of different types of CRC interventions within the same model, like comparing CRC screening with curative interventions. Almost all published cost-effectiveness analyses of screening compares one kind of CRC screening with another and not with other kinds of interventions in the health service.

Fourthly, the model can *estimate resource use*. By including the use of resources, like labor, instruments, blood, medication and beds for each procedure, the model could be used to predict the need for extra personnel or instruments for new or extended CRC treatment.

Fifthly, the model can *adjust for change in parameters over time (time-dependency)*. The model can simultaneously take into account the time since CRC treatment, consequences of the age of the CRC patients (mortality, recurrence, primary treatment cost, etc.), progress in the treatment (changes in the recurrence rate and survival, etc.) and change in cost and resource-use over time. For this, we use eight tunnels and a three-dimensional data matrix.

Sixthly, the model is *transferable* to other countries that have access to the same types of data, like the OUS data. Calibration has not been used in this model; thus, applying data from another country and building the model with the recommendations and assumptions in this article, the model should, in principle, have a similar goodness of fit.

Additionally, by using the widespread software Excel, modified versions of this type of model could also be used for other purposes. E.g. *decision makers* could use the model by changing the model inputs and gain preliminary insight about potential health benefits and costs of new emerging treatment strategies.

Tables for Appendix 1:

Table 1*. Definitions of events according to three main endpoints*

Event	**Endpoint**		
	Disease-free survival	**Time to recurrence**	**Overall survival**
Local or regional recurrence	F	F	I
Distant metastasis (DR)	F	F	I
Second primary, CRC	F	I	I
Second primary, other cancer	F	I	I
Death from CRC	F	F	F
Death from other cancer	F	C	F
Non-cancer death	F	C	F
Treatment-related death	F	C	F
Loss to follow-up	C	C	C

Failures is F, censoring is C and ignoring is I.

Table 2*. The parameters for estimating the transformation probability related to stages I–IV with R0 resection.*

Variables	Parameter for DFS curve				Parameter for TTR curve				OS for recurr.
	I	II	III	IV	I	II	III	IV	
Υ	1.113	.785	.776	.837	.977	.655	.675	.714	.797
a_0	-11.087	-6.915	-6.086	-2.362	-11.609	-5.776	-4.876	-1.695	-5.299
a_1 (age)	.068	.039	.034	-.007	.071	.026	.020	-.011	.039
a_2 (gender)	.408	.266	.251	.006	.422	.182	.150	-.268	.138

OS is overall survival, DFS is disease-free survival, TTR is time to recurrence and Υ is p in Stata. Source: OUS data.

***Table 3**. Transition probabilities from primary treatment (according to TNM stages) to other health states. For the abbreviation in the first column, see also text box 1. Source: OUS.*

The probability to:	Abbrevi-ation	TNM stages			
		Stage I	Stage II	Stage III	Stage IV
Die within 30 days after surgery	$tp_{0,70}^{TNM,30d}$	.0030	.0310	.0290	.1120
Die of CRC the first year after surgery	$tp_{0,70}^{TNM,CD}$	.0016	.0108	.0270	.4185
Receive palliative treatment the first and second year after treatment	$tp_{0}^{TNM,Pa}$	.0000	.0000	.0000	.3718
Be considered disease-free the first year after treatment	$tp_{0,70}^{TNM,TNMc}$	.9646	.8479	.7766	.0375
Get a local recurrence during the first year after treatment	$tp_{0,a}^{TNM,LR}$	.0029	.0122	.0100	.0007
Get both local and distant recurrence during the first year after treatment	$tp_{0,a}^{TNM,LDR}$	.0007	.0061	.0149	.0010
Get a distant recurrence during the first year after treatment	$tp_{0,a}^{TNM,DR}$	.0117	.0626	.0985	.0074

***Table 4**. Conditional probabilities for estimating transition probabilities related to recurrence, given that the patients have received a R0 surgery.*

The probability of:	Abbrevi-ation	Stage I	Stage II	Stage III	Stage IV
Getting a recurrence (during the year of primary treatment) according to TNM stages, given R0 surgery for the primary CRC	REC_{TNM}	.0177	.0994	.1665	.3668
Getting a R0 surgery according to TNM stages	$R0_{TNM}$	1.000	.957	.943	.059
Having a local recurrence (LR) (during the year of primary treatment) according to TNM stages, given a recurrence (R) and R0 surgery for the primary CRC	$LRofR_{TNM}$	.190	.151	.081	.081
Having a local and distant recurrence (LDR) (during the year of primary treatment) according to TNM stages, given a recurrence (R) and R0 surgery for the primary CRC	$LDRofR_{TNM}$	.048	.075	.121	.108
Having a distant recurrence (DR) (during the year of primary treatment) according to TNM stages, given a recurrence (R) and R0 surgery for the primary CRC	$DRofR_{TNM}$	.762	.774	.798	.811
Dying during the first month after being diagnosed with the first recurrence	$CD_{TNM+REC}$	.088	.107	.172	.536
Dying of CRC in the period two to twelve months after the primary treatment, given that the patient got a recurrence this year	CD_{REC30d}	.0422	.0422	.0422	.0422

Table 5*. Transition probabilities from the first year of recurrence to other health states the next year. For the abbreviation in the second column, recall Box 1. Source: OUS.*

The probability of:	Abbrevi-ation	Type of recurrence the patient are leaving (REC)		
		Local recurr.	Local & distant	Distent recurr.
Dying of CRC the first year after recurrence	$tp_0^{REC,CD}$	.2234	.5934	.4334
Receiving palliative treatment the first and second years after recurrence	$tp_0^{REC,Pa}$	.6035	.3600	.3853
Being considered disease-free the first year after recurrence	$p_0^{REC,RECc}$	.1030	.0	.1097
Getting a local recurrence the first year after being treated for recurrence	$p_0^{REC,R-LR}$	.0019	.0	.0
Getting both a local and distant recurrence the first year after being treated for recurrence	$p_0^{REC,R-LDR}$	.0025	.0	.0
Getting a distant recurrence the first year after being treated for recurrence	$p_0^{REC,R-DR}$	.0191	.0	.0251

***Table 6**: Transition probabilities for patients moving through the model after being "disease free" for the first recurrence or later recurrences. "Disease free" means that there is still no sign of CRC after a R0 resection after recurrence (or later recurrences).*

The number of years "disease free" after the year of R0 resection for recurrence or later recurrence		Probability of moving to state of new recurrence (local = R-LR, distant = R-DR, both = R-LDR) or dying					From one year to the next in the "disease free tunnel" †
		R-LR	R-DR	R-LDR	CRC Mortality*	No CRC Mortality	
Move from	Disease free year 1	.0166	.1662	.0221	.0090	.0391	.7468
	Disease free year 2	.0162	.1618	.0215	.0088	.0444	.7473
	Disease free year 3	.0157	.1570	.0209	.0085	.0479	.7500
	Disease free year 4	.0152	.1521	.0203	.0083	.0510	.7532
	Disease free year 5	.0147	.1473	.0196	.0080	.0538	.7565
	Disease free years 6, 7, etc.	.0143	.1427	.0190	.0078	.0434	.7729

** : The estimates show the probability of getting a recurrence and dying within one month (see also the text).*

†: The estimates show the transition probabilities moving from one year of being disease-free to the next year of being disease-free (the probability of staying in the tunnel from one year to the next), that means the probability of staying "cured" another year.

Table 7*. Frequency per-patient and values per-unit for primary treatments, used within the base case model analysis. The frequencies show how many times the average patient with a certain diagnosis receives the treatment stated (see also the text). Treatment for recurrence is not included.*

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 tumor							
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-resectional surgery							
Endoscopic therapy colon; closure stoma, w (152, S)	5	.0	.0	.045	.026	9,539	NPR
Endoscopic therapy colon; closure stoma, n (153, S)	6	.036	.036	.090	.026	6,758	NPR
Endoscopic therapy rectum; TEM, w (157, S)	7	.0	.0	.0	.101	5,519	OUS
Endoscopic therapy rectum; TEM, n (158, S)	8	.0	.0	.0	.034	2,748	OUS
GI obstruction, w (180, S)	9	.0	.0	.0	.044	3,939	OUS
GI obstruction, n (181, S)	10	.0	.0	.0	.015	2,140	OUS
Endoscopic/other treatment							
Digestive malignancy, w (172, M)	11	.0	.107	.493	1.526	7,526	NPR
Digestive malignancy, n (173, M)	12	.0	.0	.164	.184	4,409	NPR
Aftercare and rehabilitation (465)	13	.0	.0	.030	.553	6,207	NPR
Endoscopic insertion of stent to	14	.0	.0	.0	.008	1,310	OUS

gastro. tract, short therapy (703O)							
Treatment for metastasis							
Resection							
Liver metastasis resection, w (191B, S)	15	.0	.0	.0	.125	26,528	(23),(20), (41),(42)
Lung metastasis resection (75, S)	16	.0	.0	.0	.019	18,968	(23),(42)
No-surgical supportive treatment and care							
Liver metastasis (203, M)	17	.0	.0	.0	.188	6,468	NPR, exp
Lung metastasis (82, M)	18	.0	.0	.0	.075	7,664	NPR, exp
Chemo- and radiotherapy							
Radiotherapy (409E, M)	19	.033	.075	.147	.056	645 *	(28, 45), exp
Palliative chemotherapy (M)	20	.0	.0	.0	.610	20,183 †	(43, 45-48)
Adjuvant chemotherapy (M)	21	.0	.054	.535	.05	8,677/ 7,494	(43, 45-48)

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 (27)

**: Cost per visit at hospital for radiotherapy*

†: The cost first year of palliative treatment

Table 8. *Examinations before surgery (all stages) and follow-up during primary treatment and the following years, compliance, cost per unit and data source.*

Examination	Before surgery	Follow up, stage II and III (stage IV)							Cost/ unit (€)	Source unit cost
		Prim. treat.	Y.1	Y 2	Y 3	Y 4	Y 5	Comp		
Outpatient consultation	1	3 (3)	2(2)	2(2)	1(2)	1(2)	1(2)	1	308	DRG
CT abdomen/liver/ pelvis ("bekken")	1	1 (3)	(2)	(2)	(2)	(2)	1(2)	0.85	411	Marked
Colonoscopy	1	1 (1)					1	0.57	289	DRG
CEA-test	1	2 (3)	2(2)	2(2)	1(2)	1(2)	1(2)	0.63	16	Marked
Ultrasound, rectum	ReCa								128	Marked
MRI, rectum	ReCa								250	Marked
Biopsy	1								494	DRG
Proctoscopy		ReCa			ReCa	ReCa	ReCa	0.57	251	DRG
CT scan lungs			1	1	1	1		0.85	141	Marked
CT scan liver			2	2	1	1		0.85	193	Marked

"ReCa": only rectal cancer

"Marked": price per unit was based on the private market of health service in Norway

"Comp.": compliance for following up

***Table 9**. The costs of different components of the palliative chemotherapies (euro).*

Components in the treatment	5-FU/FA	Bevacizumab + FLIRI	Bevacizumab + FLOX	FLIRI		FLOX		EGFR + irinotecan
				1. line	2. line	1. line	2. line	
Medicine (from pharmacy)	3,081	32,734	31,772	5,789	4,211	5,083	3,697	30,873
Administered in hospital	479	1,197	1,197	439	319	878	638	2,154
CT-scanning	1,029	1,179	1,179	943	686	943	686	2,831
Out-patient consultation	1,497	1,834	1,834	1,384	1,047	1,384	1,047	2,171
Side effects*	1,121	1,699	1,699	1,072	925	1,072	925	1,548
Sum cost	7,206	38,643	37,681	9,627	7,188	9,360	6,993	39,577

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

Figure:

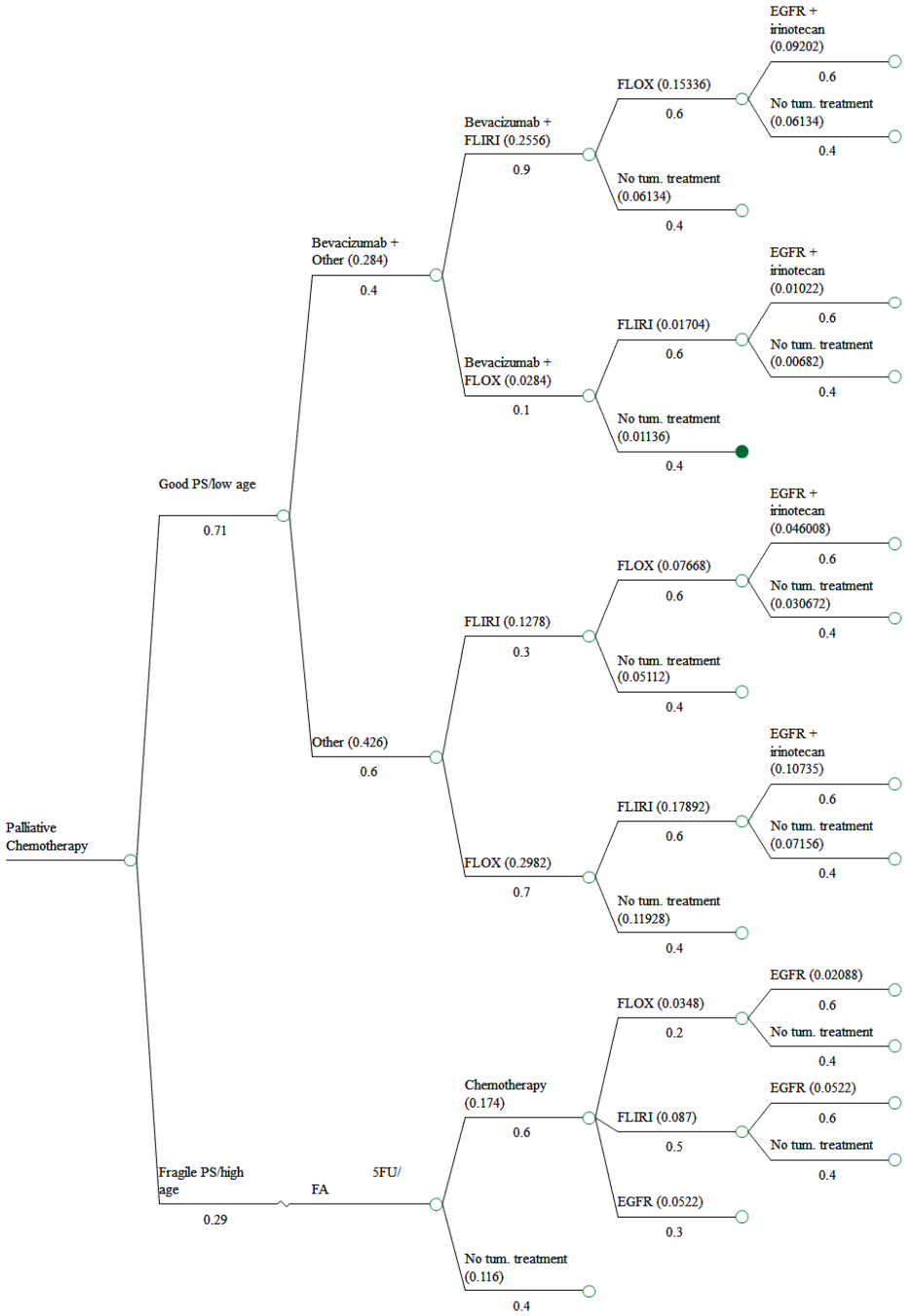

Figure 5. The decision tree for patients treated with palliative chemotherapy (61% of all stage-IV patients).

Textbox:

Textbox 1.

The Markov model was based on transition matrixes with the following notation:

$$tp_{t,a}^{f,s} = tp_{time\ in\ tunnel,age}^{from,to}$$

f = the health state from which the patient was moving

s = the health state to which the patient was moving

t = number of years (time) the patient has been in the tunnel

t = 1, 2…10

t = 0, the patient had not entered a tunnel, but was in one of the treatment states

a = the age of the patient leaving a health state

The abbreviations for *health states*:

TNM (I, II, III or IV): TNM stages defining primary treatment the first year after CRC-diagnosis

REC (LR, DR or LDR): Treatment states for recurrence; local (LR), distant (DR) and both local and distant recurrence (LDR)

R-REC (R-LR, R-DR or R-LDR): Treatment states for re-recurrence or later recurrence

c: Referring to "*disease free"* after primary resection *or "disease free"* after REC (a supplement, like IIIc, DRc or R-DRc)

D: Death by all causes other than CRC

30d: Death within 30 days after surgery

CD: Death by CRC more than 30 days after surgery

Pa: Palliation