

What is the real-world incremental cost-effectiveness ratio of combination chemotherapy over sequential chemotherapy in the treatment of metastatic colorectal cancer patients that are not eligible for curative treatment?

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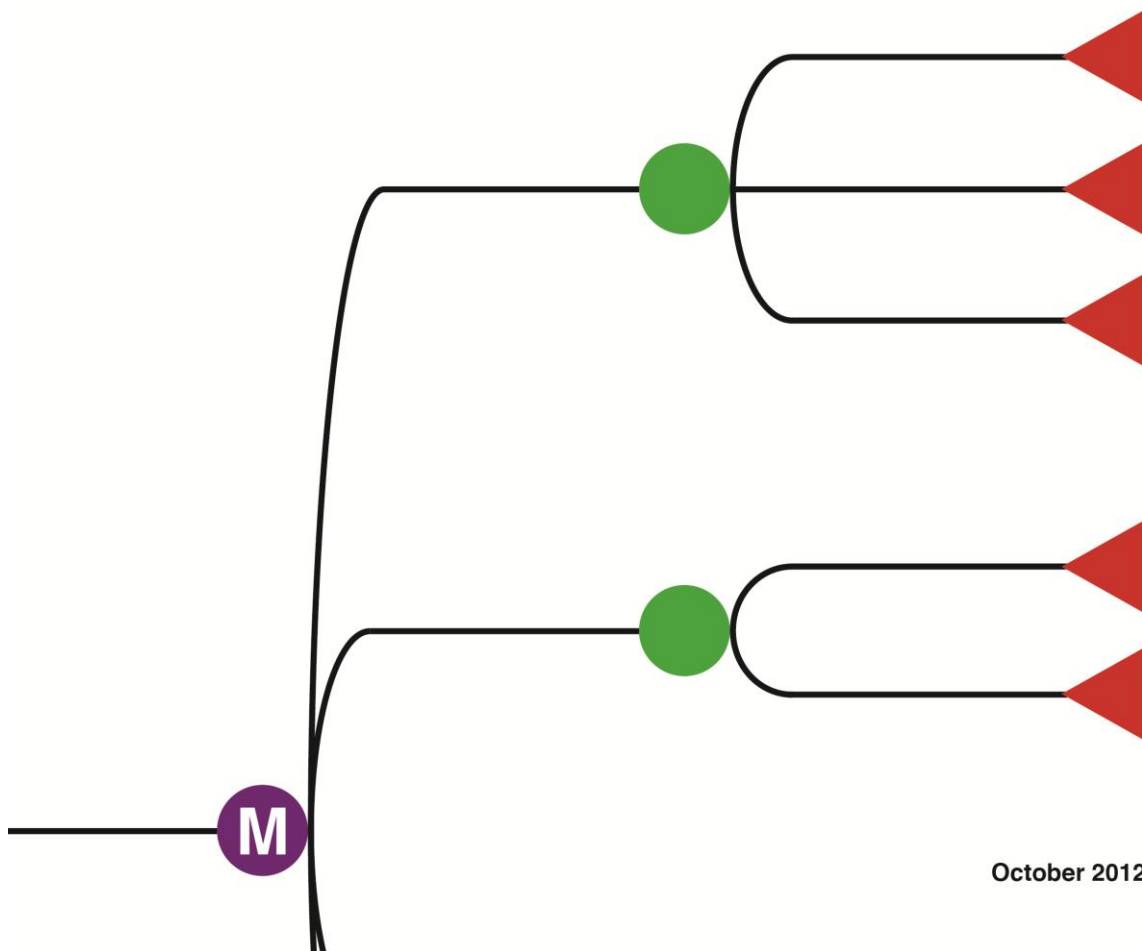


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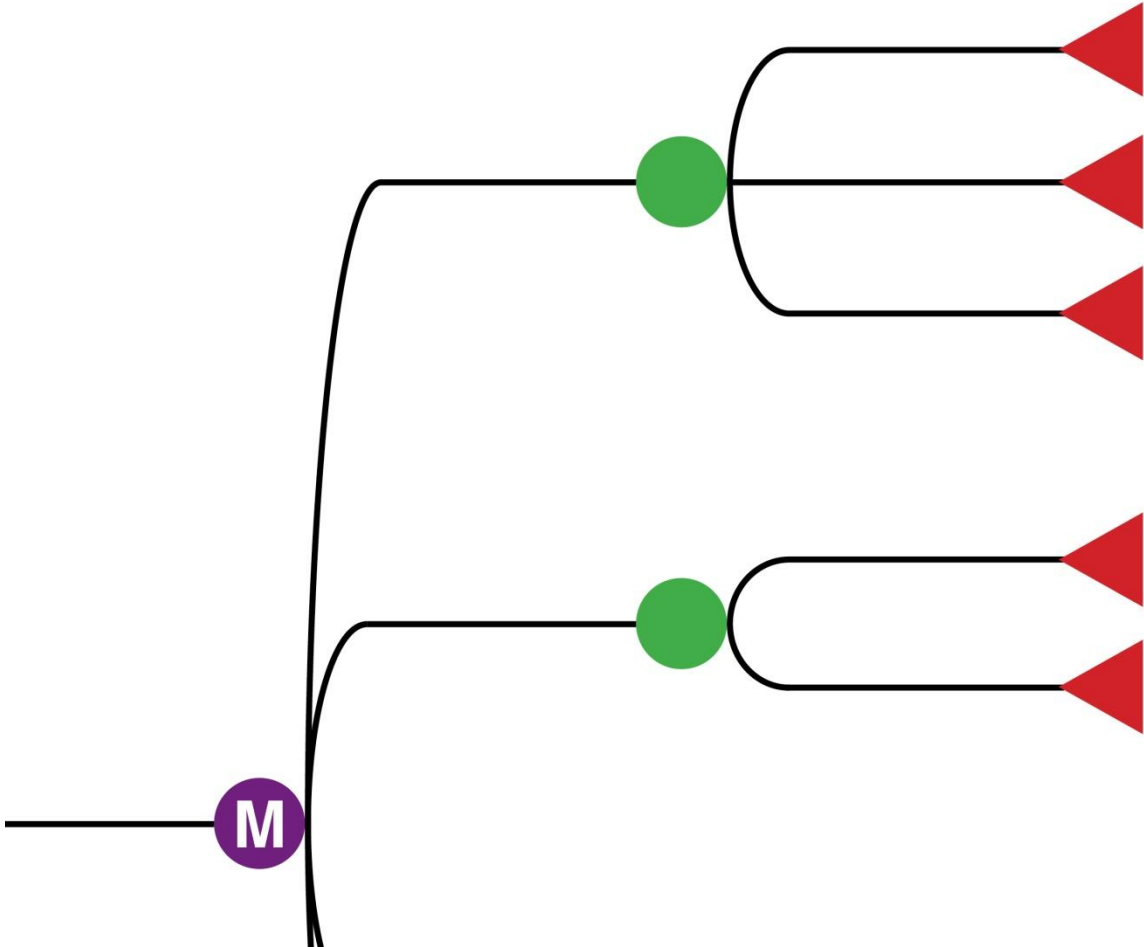
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Used Abbreviations

5-FU	5-fluorouracil
5-FU/LV	5-fluorouracil with leucovorin
AE	Adverse events
ANOVA	Analysis of variance
CAPIRI	Capecitabine with irinotecan
CAPOX	Capecitabine with oxaliplatin
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CRF	Case record form
CVZ	College voor zorgverzekeringen (Dutch healthcare insurance board)
DCCG	Dutch Colorectal Cancer Group
IKC	Integraal kanker centrum (Dutch cancer registry)
FL	Fluoropyrimidines
FOLFOX	Infusional 5-FU/LV with oxaliplatin
FOLFIRI	Infusional 5-FU/LV with irinotecan
HR	Hazard ratio
HRQoL	Health-related quality of life
iMTA	Institute for Medical Technology Assessment
ITT	Intent-to-treat
LV	Leucovorin
mCRC	Metastatic colorectal cancer
NICE	National institute for health and clinical excellence
NZa	Nederlandse zorgautoriteit (Dutch healthcare authority)
OS	Overall survival
OSA	One-way sensitivity analysis
PFS	Progression-free survival
PSA	Probability sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
UFT	Uracil/tegafur
WTP	Willingness-to-pay

1 Introduction



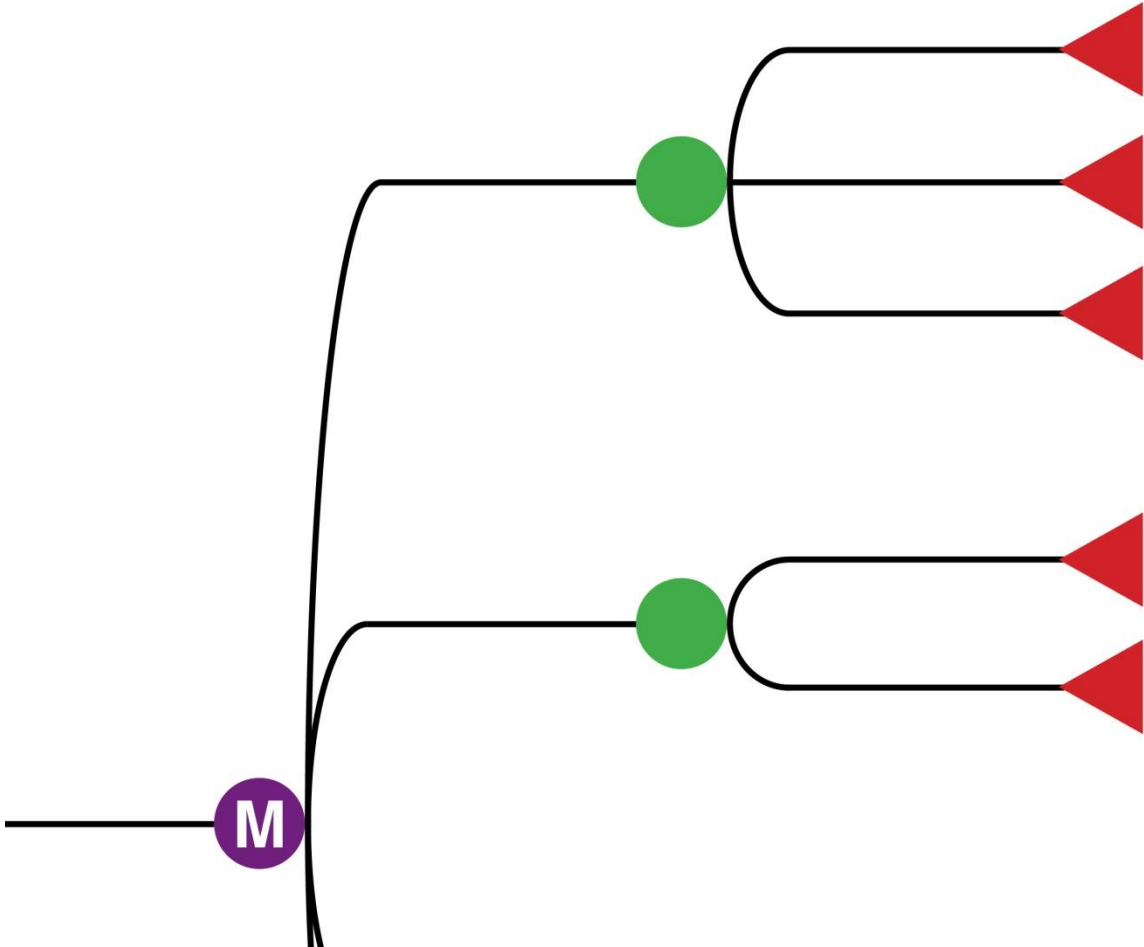
In 2009 there were 12,500 new colorectal cancer cases diagnosed in the Netherlands, in the same year 4,861 people died as a consequence of colorectal cancer. Colorectal cancer is divided into four stages with stage I as least severe and stage IV as an incurable or terminal state. Nineteen percent of the patients have stage IV colorectal cancer, also known as metastatic colorectal cancer (mCRC), at diagnosis. For most mCRC patients no curative treatment option is left. The life expectancy without a curative treatment is less than 20 months with the best combination of chemotherapeutic treatments.

In this thesis a cost-effectiveness analysis has been done for chemotherapy in the treatment of metastatic colorectal cancer (mCRC). Some chemotherapeutic drugs that are used for the treatment of mCRC are covered by the Dutch policy regulation of expensive medication. The regulation reimburses expensive medication under condition of daily practice outcome research every four years. Currently the Dutch healthcare insurance board considers to abolish the reimbursement of the medications for two rare diseases, since the medications were stated as not cost-effective enough in daily practice. This has created an extensive discussion in the Dutch society about the entitlement to healthcare and the right to withdraw reimbursement based on cost-effectiveness analysis.

The aim of this thesis is to answer the following research question: *What is the real-world incremental cost-effectiveness ratio of combination chemotherapy over sequential chemotherapy in the treatment of metastatic colorectal cancer patient that are not eligible for curative treatment?*

Therefore the model for cost-effectiveness analysis used in the CAIRO trial and oxaliplatin outcome research has been changed. Changing the model can change the outcomes and conclusions. Cost-effectiveness analysis is an increasingly important method in the Dutch healthcare system to control healthcare expenditure. The budget impact of healthcare expenditure is rising and reached 14.9% of the GDP in 2011.¹ Therefore more and more choices have to be made in reimbursement of medical treatments.

Summary



Background

Treatment of mCRC patients has evolved from 5-FU monotherapy as the only accepted therapy in the 1960s, till 2012 were a combination of chemotherapy regimens and targeted therapy is the standard. In this thesis only mCRC patients that are ineligible for curative treatment are included. These patients were treated with the chemotherapeutic drugs fluoropyrimidine, oxaliplatin or irinotecan in 2003 and 2004. There are different common combination with these drugs which can be divided in the sequential and the combination treatment arms

Cost-effectiveness

The CAIRO trial was a non-inferiority open-label, phase III randomised controlled trial done by the DCCG. Sequential versus combination chemotherapy in mCRC was tested. Median OS was longer for combination therapy and it was associated with an improvement in PFS in first line treatment compared to sequential therapy, but both differences were not significant. A higher percentage of the sequential treatment group did not receive all the different drugs than of the combination treatment group, which would favour upfront combination therapy.

The oxaliplatin pilot outcome research was a retrospective daily-practice outcome research done by the iMTA at the request of the CVZ. This study investigated the appropriate use and cost-effectiveness of oxaliplatin in Dutch daily practice for the treatment of mCRC. The aim of this research was to investigate the appropriate use of oxaliplatin in daily practice.

Methods

The data source was patient level data, collected for the oxaliplatin outcome research of newly diagnosed stage IV colorectal patients in 2003 and 2004 in the Netherlands. The incremental cost-effectiveness ratio of combination chemotherapy over sequential chemotherapy was investigated. The transition probabilities were calculated from the patient level data that were available. The chemotherapy costs are calculated using the patient level treatment information. As patient level data of costs was not available, these were calculated as a weighted average from the total costs reported in the outcome research. Costs related to end-of-life care were calculated based on literature. The retrospective design of this study made it impossible to collect quality-of-life data. This data was abstracted from the oxaliplatin outcome research which used the data collected in the CAIRO trial.

Results

The median OS in the sequential treatment arm was 11.2 months and 19.1 months in the combination treatment. The ICER of combination treatment compared to sequential treatment was € 49,172 per QALY gained and € 39,373 per LY gained. The combination treatment arm was 0.53 QALY more effective than the sequential treatment arm but also € 26,022 more expensive.

The impact of the model parameters on the model were evaluated using a USA and a PSA. The OSA showed that chemotherapy costs of combination treatment was the parameter that effected the ICER the most, followed by the total other costs of combination treatment. In the PSA 71% of the 10.000 iterations the ICERs of the combination treatment are stayed under the WTP of € 50.000 per QALY gained.

Discussion

In both the CAIRO trial and the outcome research no ICERs were calculated for stage IV patients. Comparison therefore will focus on OS and costs.

In this thesis eligible and ineligible patients were combined, resulting in a median OS of 11.2 months for sequential and 19.1 months for combination treatment. The median OS for sequential therapy was the highest in the CAIRO trial (16.3 months), followed by the median OS of this thesis and the outcome research (both 11.2 months). For combination treatment the OS of this thesis was the highest (19.1 months), followed by the CAIRO trial (17.4 month) and lowest for the outcome research (15.1 month). The difference in OS for combination treatment between this thesis and the outcome research was already expected, since the OS of the patient population used as this thesis input was already higher.

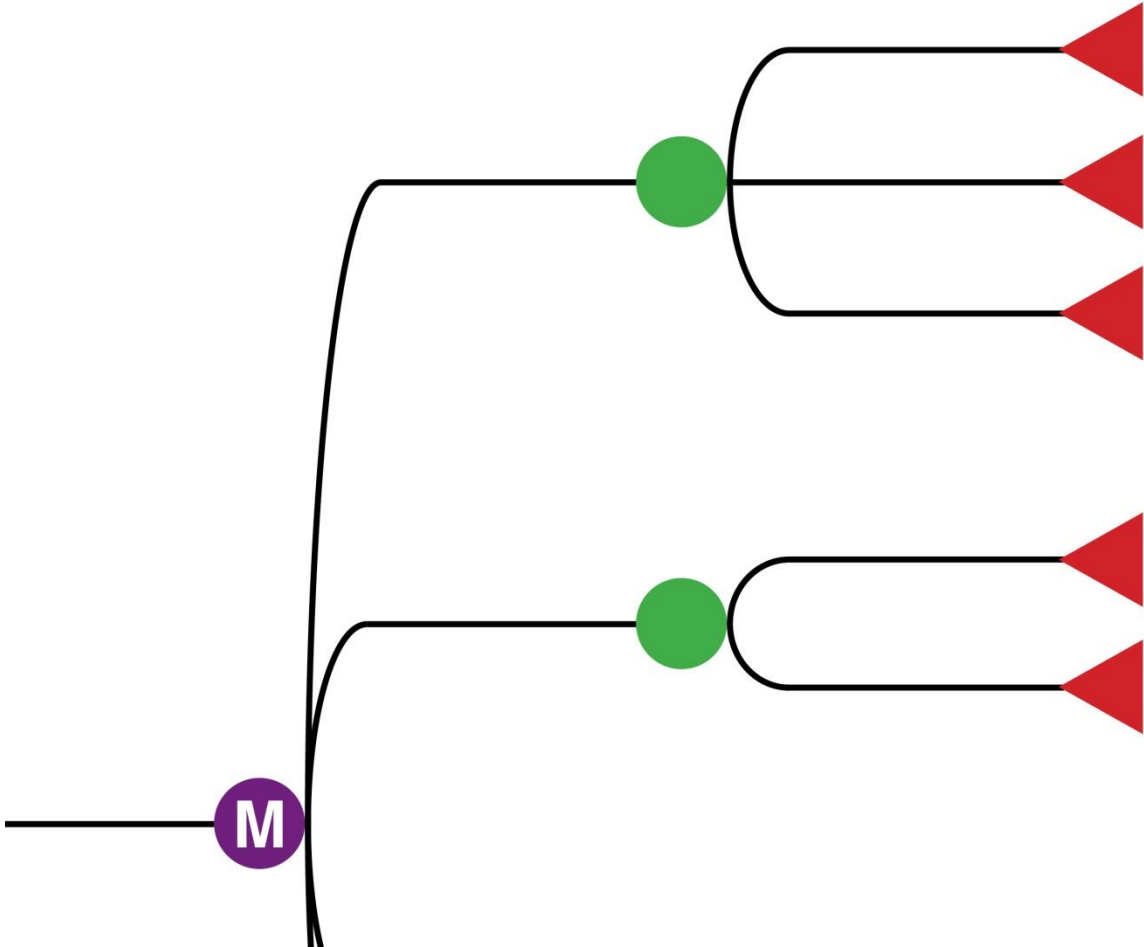
The total mean costs for the outcome research were € 19,812 for monotherapy, € 28,200 for oxaliplatin combination treatment, € 44,664 for irinotecan combination treatment and € 13,899 for ineligible patients. The total costs as in this thesis were € 24,336 for sequential and € 50,358 for combination treatment arm. The costs in this thesis are higher than the costs in the outcome research. The effects of this thesis were also higher than found in the outcome research. Since there was no ICER calculated in the CAIRO trial or outcome research no comparison can be made.

Conclusion

The aim of this thesis was to investigate the real-world ICER of combination over sequential chemotherapy in the treatment of mCRC patients that are ineligible for curative treatment.

In the CAIRO trial there was concluded that it is more important that patients are exposed to all three types of chemotherapeutic drugs, than that they are treated in the combination or sequential treatment arm. In this thesis there is shown that combination treatment has an higher median OS than sequential treatment. This increase in OS comes with higher costs, but the ICER of combination over sequential treatment does not exceeds the WTP of € 50,000 per QALY gained. Since the higher OS increases the change that patients are exposed to all three chemotherapeutic drugs, upfront combination treatment is preferred.

2 Background



2.1 Metastatic colorectal Cancer

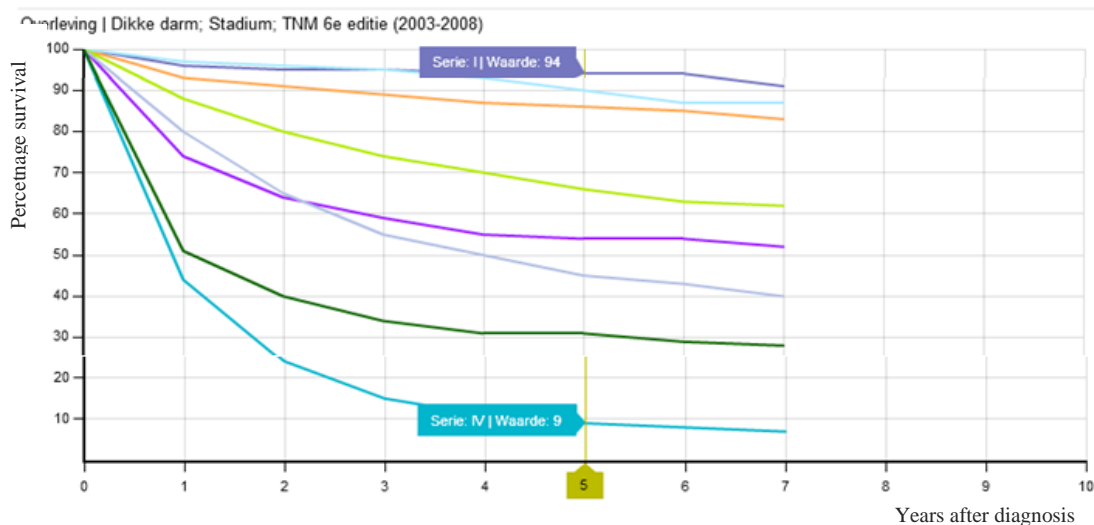
Colorectal cancer usually develops from a polyp of the mucous membrane that lines the intestines. Polyps are mostly benign, but in time they can develop into cancer. Colon cancer is divided into four stages. Stage I and II are colorectal carcinomas confined to the wall of the colon and/or rectum. If the carcinoma extends to the regional lymphatic glands it is termed stage III colon cancer. In stage IV colorectal cancer, also known as metastatic colorectal cancer (mCRC), the carcinoma has spread beyond the lymph nodes to distant sites.

2.2 Epidemiology

In 2009 colorectal cancer was the cause of 4,861 deaths in the Netherlands, 11.8% of the total number of deaths due to cancer. The prevalence of mCRC is still rising due to a slowly increasing incidence, the age of the population and the increasing survival of the colorectal patients. The number of diagnosed patients is expected to rise to about 14,000 in 2015.² The mortality of colorectal cancer as a percentage of total mortality per gender is higher among women (12.21%) than among men (11.39%). But among men it takes second place after lung cancer (28.53%) and among women it takes third place after lung (18.80%) and breast cancer (16.92%).³

In 2009, approximately 12,500 new colorectal cancer cases were diagnosed. Four percent of the new diagnosed cases were not classified. Stage I and II comprise 40% of all colorectal cancer cases at diagnosis, stage III comprises 37%. Approximately 19% of newly diagnosed cases have metastatic disease and approximately half of newly diagnosed patients in other stages will end up progressing to stage IV as well. Of the 19% newly diagnosed mCRC patients only the patients that are not eligible for surgery were included in both used trials and in this thesis.⁴

Figure 1. Five year overall survival of colorectal cancer.



Source: Integraal Kankercentrum Nederland

Generally, only a few patients with metastatic disease, approximately 9%, have an overall survival (OS) of five years. In comparison, for patients diagnosed with stage I colorectal cancer the five-year OS is approximately 94%, see Figure 1.⁵

2.3 Treatment of metastatic colorectal cancer

2.3.1 Aim of the treatment of metastatic colorectal cancer

The aim of treatment of mCRC is to prolong the progression free survival (PFS) and OS and to maintain the quality of life (QoL) as best as possible.

2.3.2 Current management of metastatic colorectal cancer

The treatment of colorectal cancer depends on the stage of the disease and the patient's overall physical health. In the treatment of stage I, II and III surgery plays a central role. Treatment has a curative intent in these stages. However, in mCRC, the treatment is mainly focused on increasing PFS and OS and maintaining the QoL, since stage IV is incurable in most cases. Systemic treatment options for mCRC consist of chemotherapy in sequential or combination treatment.^{6, 7}

Surgery

For most mCRC patients surgery is not a curative treatment option. For patients with stage I, II, and III colorectal cancer, surgery, with or without adjuvant chemotherapy, is the recommended treatment option. Nearly half of the patients who undergo curative surgery will eventually relapse and finally die of mCRC.^{8, 9} In stage IV the carcinoma has spread to distant sites, which make surgery difficult. A small group of patients constitute an exception; for patients with very few, clearly defined metastases, surgery can be a curative option. For all other patients with mCRC removing the primary tumour can be an additional part of the standard treatment with chemotherapeutic regimens, in order to increase the PFS and the OS.

In this thesis the term mCRC patients indicates the patients that are diagnosed with mCRC and who are ineligible for additional surgery. The patients that are eligible for additional surgery are excluded of the thesis' patient population.

Systemic therapy

Chemotherapy is the backbone of mCRC treatment. The optimum order and combination of chemotherapeutic drugs for mCRC has not yet been defined. Treatment with a combination of drugs is preferred. The patient's overall health status and both the patient's and the clinician's preference are decisive for the choice of one combination over another combination of chemotherapeutic drugs.

2.3.3 Chemotherapy

Chemotherapy as treatment for cancer was originally discovered as a side effect of the chemical warfare agent Mustard gas during World War I. Accidentally exposed people were later found to have a very low amount of white blood cells. Doctors reasoned leukaemia patients could benefit of the inhibition of the production of white blood cells. In further research, Mustard gas was administered to several patients with advanced lymphomas in the 1940s. The patients improved markedly, but temporarily, because the production of white blood cells increased again over time. Since then a lot of research has been done and improvement has been made. The result is a wide range of chemotherapeutic drugs.¹⁰ In 2003 and 2004, when the study data was collected, standard treatment for mCRC included three chemotherapeutic drugs; fluoropyrimidines, irinotecan and oxaliplatin. Meanwhile other therapies are developed; bevacizumab, cetuximab and panitumumab. These therapies are not included in this thesis and are therefore not further discussed. Fluoropyrimidines, irinotecan and oxaliplatin vary in their chemical composition, administration and side effects. The basic characteristics of the three drugs can be found in appendix A.

2.3.4 Treatment of metastatic colorectal cancer in daily practice

For the purpose of this thesis, the treatment of mCRC patients is divided in three subsequent treatment phases; first, second and third line treatment. This division is taken from the oxaliplatin outcome research. Patients transfer from first to second or from second to third line treatment after disease progression, after discontinuation of the previous treatment line or after unacceptable toxicity.

Table 1. Possible (equivalent) treatment options.

	First line	Second line	Third line		Treatment	CAIRO
A	FL	FL + oxaliplatin	(FL +) irinotecan		Sequential	-
B	FL	(FL +) irinotecan	FL + oxaliplatin		Sequential	✓
C	FL + oxaliplatin	(FL +) irinotecan			Combination	-
D	(FL +) irinotecan	FL + oxaliplatin			Combination	✓

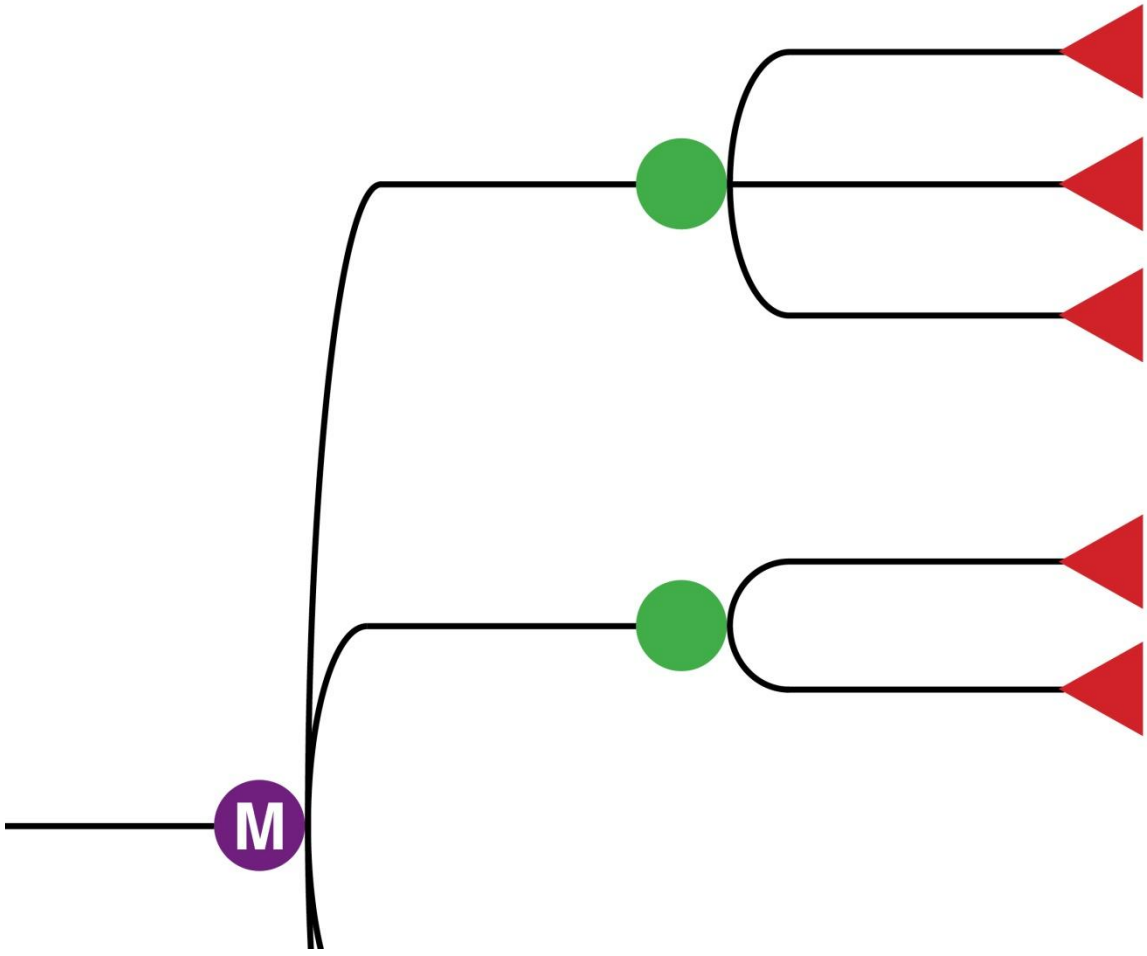
Table 1 shows the most common treatment possibilities for chemotherapy per line of the different treatments used in Dutch daily practice in 2003-2004. Treatment A and/or B are named sequential treatment. Treatment C and/or D are named combination treatment.

Not postponing systemic therapy is the main message of the Dutch guideline for the treatment of mCRC. If patients health status tolerate, first line combination treatment with fluoropyrimidines and either oxaliplatin or irinotecan is preferred. The guideline states that the median OS for either sequential or combination treatment of fluoropyrimidine with irinotecan or oxaliplatin is equivalent.^{11, 12}

After first line monotherapy with FL (treatment A or B) there is no difference in median OS between FL+ox and FL+iri. The choice for FL+ox can be made based on a higher response rate in second line treatment. Third line treatment with FL+ox was based on the choice made for second line treatment; if second line treatment was FL+iri then treatment with FL+ox was left for third line treatment.^{13,14} The decisions about the sequence of drugs that are administered will be made based on the clinician's preferences.

The use of both FL+ox and FL+iri in sequence, resulted in a median OS that exceeds 20 months.¹⁵ The exposure to all three cytotoxic drugs (FL, irinotecan and oxaliplatin) during the course of the treatment is more important than receiving a specific drug in the first line.¹⁶ But not all patients go through all treatment lines; approximately 50 to 80% of the mCRC patients receive a second line therapy, 20 to 50% of the patients discontinued their treatment or died before reaching second line treatment. Therefore treatment in first line therapy can be very important, since for many patients it is their only exposure to chemotherapy.

3 Clinical- and cost-effectiveness



A lot of research has been done on the treatment of colorectal cancer in general. Especially since there is still no curative treatment for mCRC. This chapter addresses both clinical evidence and the evidence of daily practice use of fluoropyrimidines, oxaliplatin and irinotecan in the Netherlands.

The CAIRO trial provides information about the clinical effectiveness of the three chemotherapeutic regimens in both sequential and combination therapy of mCRC. The outcome research provides real life information on patients receiving either sequential or combination therapy. Where the choice between sequential and combination therapy is made based on randomization in the CAIRO trial, it is based on daily practice decisions of physicians in the outcome research.

A summary of both the CAIRO trial and the oxaliplatin outcome research are provided here, since the health economic model of this thesis is based on both studies.

3.1 CAIRO trial

3.1.1 Design and methodology

The CApecitabine, IRinotecan, Oxaliplatin (CAIRO) trial was a non-inferiority open-label, phase III randomised controlled trial done by the Dutch Colorectal Cancer Group (DCCG). Sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer was tested. The aim of the CAIRO trial was to investigate whether combination therapy was superior to the sequential administration of the same drugs in the treatment of mCRC patients.

Patients were enrolled between January 2003 and December 2004. All patients who met the inclusion criteria were randomised to receive either sequential or combination therapy. Sequential therapy consisted of first line capecitabine, second line irinotecan, and third line capecitabine plus oxaliplatin. Combination therapy consisted of first line capecitabine plus irinotecan and second line capecitabine plus oxaliplatin. Both treatment arms are shown in Table 2.

Table 2. Treatment arms in CAIRO trial.

Treatment arm	First line	Second line	Third line
sequential	Capecitabine	irinotecan	capecitabine + oxaliplatin
combination	capecitabine + irinotecan	capecitabine + oxaliplatin	

A total of 820 patients from 29 selected hospitals in The Netherlands were randomised to receive either sequential therapy (410) or combination therapy (410). Seventeen patients were found to be ineligible and were excluded from the analysis; resulted in 401 patients in the sequential and 402 patients in the combination therapy arm. Analyses were done by intention-to-treat, the primary endpoint was OS, secondary endpoints were PFS, response rate, toxicity and QoL.¹³

3.1.2 Criteria and patient population

Patients were included in the CAIRO trial using the inclusion and exclusion criteria (appendix B). There was no meaningful difference between the two treatment groups in demographics or baseline characteristics. The baseline characteristics are shown in Table 3. Of the patients randomised to intent-to-treat (ITT), 63% were male and 22% were 70 years or older. The median age at randomization was 63.0 years (range 27 – 84 years). The majority of patients (95%) had a baseline WHO performance status of 0 or 1. The predominant location of metastases was in the liver; in 70% of the cases. The site of the primary tumour was the colon in 60% of the cases. Eighty-six per cent of the patients did not have prior adjuvant therapy.

Table 3. Baseline characteristics of randomised eligible patients in the CAIRO trial.

	Sequential treatment (N=401)	Combination treatment (N=402)	Total (N=803)
Age			
Age at randomisation (years)	64.0 (27-84)	63.0 (31-81)	63.0 (27-84)
>70 years	93 (23%)	81 (20%)	174 (22%)
Sex			
Male	252 (63%)	255 (63%)	507 (63%)
Female	149 (37%)	147 (37%)	296 (37%)
Performance status			
PS0	257 (64%)	244 (61%)	501 (62%)
PS1	126 (31%)	142 (35%)	268 (33%)
PS2	18 (5%)	16 (4%)	34 (4%)
Predominant localisation of metastases			
Liver	277 (69%)	285 (71%)	562 (70%)
Liver-only	75 (19%)	92 (23%)	167 (21%)
Extrahepatic	118 (29%)	115 (29%)	233 (29%)
Unknown	6 (2%)	2 (<1%)	8 (<1%)
LDH at randomisation			
Normal	256 (64%)	257 (64%)	513 (64%)
Abnormal	145 (36%)	145 (36%)	290 (36%)
Previous adjuvant therapy			
Yes	55 (14%)	56 (14%)	111 (14%)
No	346 (86%)	346 (86%)	692 (86%)
Site of primary tumour			
Colon	251 (63%)	227 (57%)	478 (60%)
Rectosigmoid	28 (7%)	32 (8%)	60 (8%)
Rectum	119 (30%)	141 (35%)	260 (32%)
Multiple tumours	2 (<1%)	2 (<1%)	4 (<1%)
Missing	1 (<1%)	0	1 (<1%)

Data are median (range) or n (%).

Source: Koopman, 2007

3.1.3 Treatment cycles

Of the 803 patients, 795 patients received at least one cycle of treatment. All treatment cycles were administered at intervals of 3 weeks. Before entering a new treatment line, the eligibility criteria had to be met. Appendix C shows the planned dosages of the different treatment lines, the actual doses given varies per patient. In patients over 70 years old it was recommended to start irinotecan at 75% of the planned dose, and to escalate to full dose when no serious toxicity occurred.¹⁷

In both treatment arms the treatment continued for at least 6 months, until disease progression or until unacceptable toxicity; whichever came first. Continuation of the treatment after 6 months in the absence of disease progression or unacceptable toxicity was recommended, but at the discretion of the investigator. Patients who had discontinued therapy for other reasons than disease progression or unacceptable toxicity, were re-assessed on disease status after a treatment-free interval of 3 months. If the treatment-free interval was more than 3 months at the moment the treatment was restarted, the previous treatment line had to be resumed. If the treatment-free interval was 3 months or less, the next scheduled treatment line had to be initiated.¹⁷

3.1.4 Primary and secondary efficacy measures

The primary efficacy measure was OS. Secondary efficacy measures were the following:

- PFS; progression of the tumour was assessed every 9 weeks with CT scans.
- Overall response rate; proportion of patients with confirmed partial or complete response as per the Response Evaluation Criteria for Solid Tumours (RECIST version 1).
- Toxic effects were assessed according to the US National Cancer Institute Common Toxicity Criteria, version 2.0.
- Patient health-related quality of life (HRQoL) and symptom response measured by the QLQ-C30 of the European Organisation for Research and Treatment of Cancer (EORTC); questionnaire needed to be completed one week before randomization and every 9 weeks until the end of trial.

3.1.5 Results

Median OS was longer for combination therapy than for sequential therapy with a demonstrated 6.7% improvement of the OS (16.3 vs. 17.4 months). After two year 84% of randomised eligible patients had died; 83.8% in the sequential group and 84.3% in the combination group. From all the patients in the CAIRO study that started with monotherapy only 36% were exposed to all three lines.^{13, 18} The median follow-up was 31.5 months (95% CI; 14.3 – 18.1) for the 128 patients still alive.¹⁷

Table 4. Efficacy results of the CAIRO trial

	Sequential treatment (N=401)	Combination treatment (N=402)	p value
Overall survival (months)	16.3 (14.3-18.1)	17.4 (15.2-19.2)	0.3281
1-year survival rate (%)	64% (59-69)	67% (62-72)	0.38
Progression-free survival first-line (months)	5.8 (5.1-6.2)	7.8 (7.0-8.3)	0.0002
PFS2 (months)	8.7 (8.2-9.6)	10.3 (9.3-10.8)	0.15
PFS3 (months)	10.3 (9.0-11.1)	NA	0.19*
Overall response rate (CR+PR)†			
First-line	77 (20%, 17-26%)	139 (41%, 36-46%)	<0.0001
Second-line	23 (10%, 6-15%)	24 (12%, 7-17%)	0.46
Third-line	5 (4%, 1-9%)
Disease control rate (CR+PR+SD)†			
First-line	280 (74%, 69-79%)	297 (87%, 82-90%)	<0.0001
Second-line	162 (71%, 65-77%)	121 (63%, 56-70%)	0.06
Third-line	72 (57%, 48-66%)

CR=complete tumour response. PR=partial tumour response. SD=stable disease. Data are median (95% CI), %, or n (%; 95% CI). *PFS3 in sequential group vs PFS2 in combination group. †Percentages are based on patients assessable for response.

Source: Koopman, 2007.

Based on CT scans, the median PFS in the first line was 5.8 months (95% CI; 5.1 – 6.2) for patients in the sequential group and 7.8 months (95% CI; 7.0 – 8.3) for patients in the combination group ($p = 0.0002$). The PFS was not affected when resuming previous treatment; after discontinued treatment and treatment-free interval, were ignored (6.0 months for sequential vs. 8.0 months for combination therapy). There was a significant difference in first line treatment, but not in second and third line treatment ($p = 0.15$ and $p = 0.19$).¹³

There was a significant difference in deterioration of QoL. The combination group deteriorated in their overall functioning or its separate domains (cognitive; emotional; physical; role; and social) more than the sequential group. The largest deterioration was seen in patients on combination therapy; with a median of 4 points more deterioration than patients on sequential therapy (24 vs. 20 points deterioration). Despite the significant difference in overall deterioration there was only one significant difference in the sub-domains of the QoL. This difference was for diarrhoea; 20 points deterioration for sequential compared to 28 points deterioration for combination therapy ($p = 0.002$).^{13, 17}

A total of 11 patients died with a probable relation to their treatment; 8 patients after sequential therapy and 3 patients after combination therapy ($p = 0.13$). In 9 of the 11 cases protocol violations had occurred; such as administration of irinotecan during hyperbilirubinaemia, non-adherence to guidelines for dose reduction or delay of administration of chemotherapy.¹³

3.1.6 Conclusions

The CAIRO trial is an open-label, phase III randomised controlled trial design to assess whether combination therapy was superior to sequential administration of the same drugs in the treatment of mCRC patients.

Combination therapy was associated with a clinically meaningful improvement in PFS in first line treatment compared to sequential therapy (7.8 vs. 5.8 months). The risk of progression was reduced by 33% when comparing combination therapy to sequential therapy ($p = 0.0002$). PFS was not effected when a resumed treatment after discontinued treatment or a treatment-free interval was ignored. The impact on PFS was not significantly different in the second and third treatment line ($p = 0.15$ and $p = 0.19$).

There was more deterioration in overall health status and in overall QoL of patients in the combination group relative to patients in the sequential group; the difference was only significant for diarrhoea ($p = 0.002$).

Median OS was longer for combination therapy than for sequential therapy, but not significant ($p = 0.33$); the hazard ratio (HR) was 0.92 for combination over sequential treatment. Therefore, sequential administration is not inferior to combination therapy in the treatment of mCRC patients.¹³

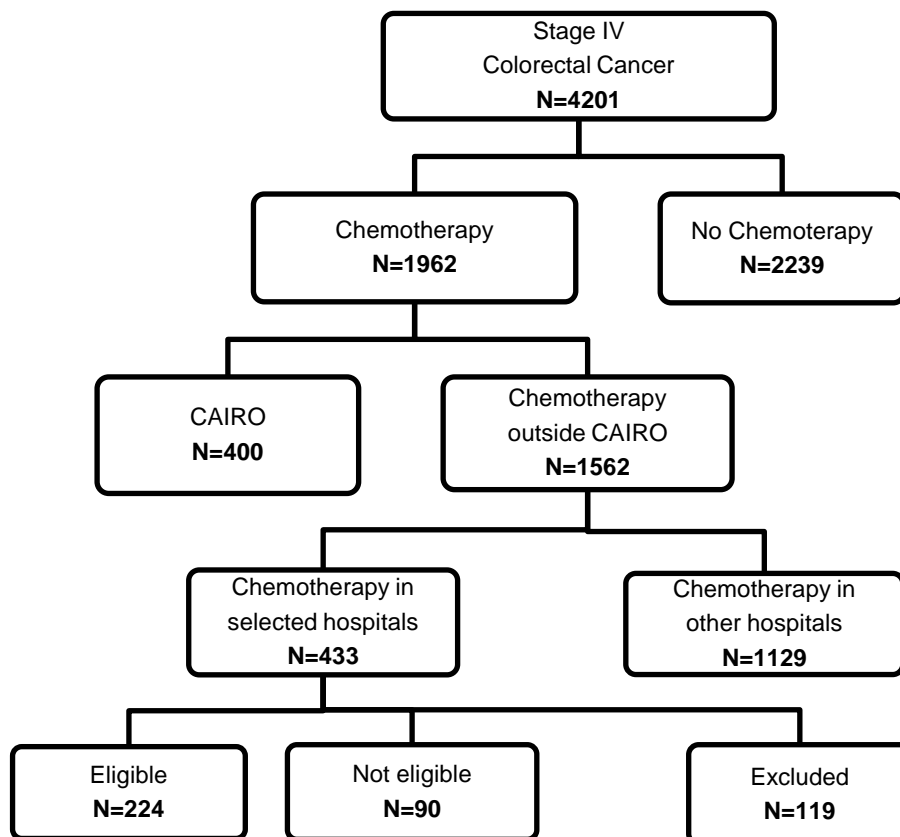
3.2 Oxaliplatin pilot outcome research

3.2.1 Design and methodology

The Oxaliplatin pilot outcome research (further named as outcome research) was a retrospective study done by the institute for Medical Technology Assessment (iMTA). The outcome research was done at the request of the Dutch healthcare insurance board (*College voor zorgverzekeringen*; CVZ) for the Dutch policy regulation of expensive medication (see appendix D for more information). The outcome research contains two sections; oxaliplatin in stage III colorectal cancer, and oxaliplatin in mCRC. In this thesis only the second section of this research was used.¹⁹ The section researched the appropriate use and cost-effectiveness of oxaliplatin by exploring how it was used in Dutch daily practice for the treatment of mCRC. The aim was to investigate the real-world effects and costs of oxaliplatin treatment.

As the outcome research is a retrospective study patients were identified in June 2007 via the database of the Dutch Cancer Registry (*Integraal kanker centrum*; IKC) and comprised patients newly diagnosed with mCRC in 2003 and 2004. More than 95% of all cancer patients in the Netherlands are registered in the database. Twenty-nine Hospitals were selected; 3 university hospitals, 14 large teaching hospitals, and 12 general hospitals (as it was considered to be a fair representation of the Dutch clinical healthcare). Twenty-five of the hospitals had also participated in the CAIRO trial.

Figure 2. Patient flowchart 2003-2004.



Source: Van Gils, 2010

Figure 2 shows the flowchart of all 4201 patients that are diagnosed with mCRC in 2003 and 2004 in the Netherlands. Of all patients 47% were treated with chemotherapy; patients that received another treatment (surgery, radiotherapy, etc.) in addition to chemotherapeutic treatment are not included in these 47%. The medical files of all 433 mCRC patients of the 29 selected hospitals in the Netherlands were reviewed, 314 patients were included and 119 patients were excluded from the outcome research. Patients were excluded because they participated in other trials (23), they had no metastases left after surgery (7), their medical files had not been reviewed (41) or their medical files were not available (48). After the evaluation, two patients were excluded because additional treatment with bevacizumab in first line treatment (one eligible and one ineligible patient) was administered; 312 patients were included for further analysis. Eighty-nine patients were found to be ineligible and were grouped separately.

Treatment assignment was not fixed or randomised; patients received either sequential (197) or combination (115) treatment.¹⁹ Patients were assigned based on their overall health status and the physicians preference.

Note that sometimes 116 patients are mentioned in the combination treatment arm in Van Gils et al.; one of the two patients that received bevacizumab was not excluded from the population systematically.

3.2.2 Criteria and patient population

The patients included in the outcome research were categorized according to the CAIRO eligibility criteria; inclusion and exclusion criteria of the outcome research are identical to the inclusion and exclusion criteria of the CAIRO trial (appendix B).

Data collection

For the collection of data three sources have been used; the database of the DCR, minimal and maximal case record forms (CRFs); all can be found in appendix E.

Disease and treatment information of all patients of the 29 selected hospitals was recorded on CRFs. The CRFs contain the information from the database of the DCR complemented with information from the patient's medical records (which were available from the 29 selected hospitals).²⁰ Patients were excluded if their medical record was not available.

Information for minimal and maximal CRFs was collected between July 2008 and March 2009. The collection was done by medical students under the supervision of the researchers. Patients were included in or excluded from the research based on the disease and treatment information in their CRFs.

Patient characteristics

Patients were first categorized according to the CAIRO eligibility criteria and thereafter to sequential or combination treatment.

Detailed treatment data was available for 11 ineligible patients and 119 eligible patients. Of the eligible patients that received combination treatment, 98% of the patients were exposed to oxaliplatin and 54% of the patients were exposed to irinotecan during their entire treatment. In comparison, 44% of the sequential treatment group was exposed to oxaliplatin and 30% of the sequential treatment group was exposed to irinotecan during their treatment. Note that in the sequential and in the combination treatment group, it was possible that patients received both oxaliplatin and irinotecan, one of these two or neither of them.

Patients on sequential treatment could only get oxaliplatin and irinotecan in second- and third line treatment. After each treatment line some patients were not able to receive further treatment, therefore the chance of receiving oxaliplatin and irinotecan was lower for patients that started on sequential treatment than for patients that started on combination treatment.

The clinical characteristics of the patient population is shown in Table 5. Fifty-nine percent of the eligible patients were male and 26% were 70 years or older. The median age of eligible patients was 61 years (range 29 - 84 years). The predominant location of metastases was in the liver in 93% of the eligible patients. The site of the primary tumour was the colon in 66% of eligible cases. Thirty-five percent of eligible patients did not have a resection of the primary tumour.

Table 5. Comparison of baseline characteristics of patients receiving chemotherapy in Dutch practice.

Baseline Characteristics	First-line chemotherapy					
	All patients N = 313			All therapies N = 313		
	mono therapy N = 197 (63%)	combi therapy N = 116 (37%)	T or X2 tests p-value m vs c	Eligible N = 224 (72%)	Ineligible N = 89 (28%)	T or X2 tests p-value el vs inel
Age - yr						
Median	64	59	<0.0001	61	63	0.96
Range	30-92	29-81		29-84	30-92	
Age group - no. (%)						
≥ 70	63 (32%)	15 (13%)	0.0002	23 (26%)	55 (25%)	0.8123
Performance status						
PS 0-1	93 (78%)	62 (90%)	0.0426	122 (92%)	33 (60%)	<0.0001
PS 2-3	26 (22%)	7 (10%)		11 (8%)	22 (40%)	
Missing	78 (40%)	69 (41%)		91 (41%)	55 (62%)	
Sex - no. (%)						
male	115 (58%)	72 (62%)	0.5206	132 (59%)	55 (62%)	0.6411
female	82 (42%)	44 (38%)		92 (41%)	34 (38%)	
Predominant localisation of metastases						
Liver	165 (91%)	94 (92%)	0.6697	191 (93%)	68 (86%)	0.0591
Extrahepatic	17 (9%)	8 (8%)		14 (7%)	11 (14%)	
Missing	15 (8%)	14 (12%)		19 (8%)	10 (11%)	
LDH at randomisation						
Normal	77 (48%)	54 (55%)	0.3401	96 (52%)	35 (49%)	0.6659
Abnormal	82 (52%)	45 (45%)		90 (48%)	37 (51%)	
Missing	38 (19%)	17 (15%)		38 (17%)	38 (43%)	
Site of primary tumor						
Rectosigmoid	19 (10%)	14 (12%)	0.157	20 (9%)	13 (15%)	0.3758
Rectum	46 (23%)	34 (29%)		56 (25%)	24 (27%)	
Colon	132 (67%)	68 (59%)		148 (66%)	52 (58%)	
Resection of primary tumor						
Yes	116 (60%)	70 (63%)	0.649	140 (65%)	46 (52%)	0.0255
No	76 (40%)	41 (37%)		74 (35%)	43 (48%)	
Missing	5 (3%)	5 (5%)		10 (5%)		

Source: Van Gils, 2010

There were two significant differences in baseline characteristics between the sequential and the combination treatment group. Among the sequential group the proportion of patients with an age above 70 was 19% higher than among the combination group ($p = 0.0002$). Ninety percent of the combination treatment group was in the two best performance status' compared to 78% percent of the sequential treatment group ($P = 0.0426$).

Costs

For the cost analysis a hospital perspective was used; costs of informal care and productivity costs were not taken into account. It was assumed that excluding these costs would not make a substantial difference, since most patients were beyond retirement age and would be equal for the different patient groups.²¹

To determinate the costs, twelve cost components were used: inpatient hospital days, intensive care days, outpatient visits, consulting by telephone, day-care treatment, emergency room visits, radiotherapy, surgical procedures, laboratory services, medical imaging services, chemotherapy and concomitant medication. Costs were calculated separately for the ineligible group, the group that received monotherapy, the group that received oxaliplatin combination treatment (first line treatment contained oxaliplatin) and irinotecan combination treatment (first line treatment contained irinotecan).

Patient level cost data was available of 130 patients; 11 ineligible and 119 eligible patients (57 on monotherapy, 51 on oxaliplatin combination treatment and 11 on irinotecan combination treatment).¹⁹

Quality of life

The retrospective study design of the outcome research made it impossible to collect HRQoL data. Both the CAIRO trial and the outcome research were done on the same source population, therefore the disease specific QoL data collected within the CAIRO trial, could also been used for the outcome research patients. Therefore a model has been used to convert the QLQ-C30 results into health utilities.²² The QLQ-C30 has 30 items divided in three categories; functional scale (15 items), symptom scale (13 items) and a global health status scale (2 items).²²

3.2.3 Treatment cycles

Table 1 (page 15) shows the different treatment options as found in Dutch daily practice in 2003 and 2004. No optimal dosage has yet been found for each type of chemotherapy, therefore not all patients included in the outcome research were given the same dosages. Started treatment type and dosage depend on patients' characteristics, hospital type, and physicians' preferences. Dosage per cycle per patient was analyzed to find differences in drugs administration between different treatment groups.

All of the 312 patients received at least one cycle of treatment. For eligible patients receiving sequential or combination treatment the median number of cycles in first line treatment was 6. In second line treatment the median number of cycles was higher for sequential treatment than for combination treatment (6 vs. 5 cycles), and in third line the median number of cycles was 3 for both. The total time on therapy varied from 1 till 37 months for sequential treatment and from 1 till 44 months for combination treatment.

Of all patients receiving first line sequential treatment, 52% received second line chemotherapy. In comparison, 62% of the patients started on first line combination treatment received second line chemotherapy. Of the patients that started on either sequential or combination treatment, approximately 20% received chemotherapy in third line.¹⁹

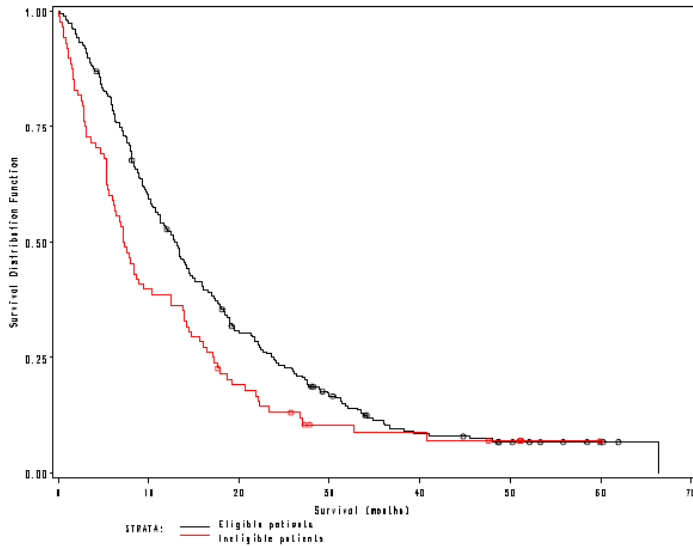
3.2.4 Primary and secondary efficacy measures

The primary efficacy measure was set the same as the CAIRO trial; overall survival. There were no secondary efficacy measures. The retrospective design of the outcome research made it impossible to collect data on HRQoL and overall response rate, therefore both are not included as outcome measures.

3.2.5 Results

The outcome research contained 312 patients. Sequential treatment was received by 63% and combination treatment by 37% of the patients. Seventy-one percent of the 312 patients were eligible. Of the 224 eligible patients 127 persons received sequential treatment and 97 persons received combination treatment in first line.

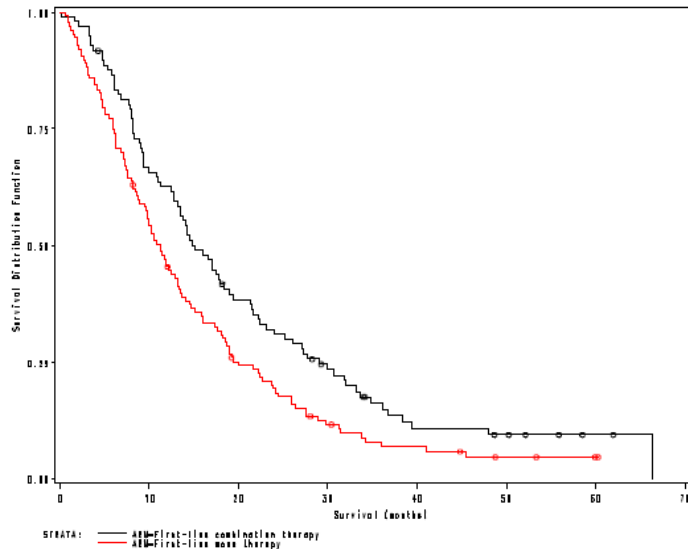
Figure 3. OS of eligible and ineligible patients.



Source: Van Gils 2010

Figure 3 shows the Kaplan Meier survival curves of both eligible (black line) and ineligible (red line) patients. The median OS was 13.1 months for eligible and 7.3 months for ineligible patients.

Figure 4. OS of sequential and combination treatment for eligible patients.



Source: Van Gils 2010

Figure 4 shows the Kaplan Meier survival curves of both sequential (red line) and combination (black line) therapy of eligible patients. Eligible patients receiving combination treatment had a median OS of 15.1 months, compared to a median OS of 11.2 months for patients receiving sequential treatment.

Twenty-six percent of the eligible patients was over 70 years old, compared to 25% of the total patient population. Thirty-two percent of the eligible patients receiving sequential treatment was over 70 years old, compared to 13% of the eligible patients receiving combination treatment. Age could be a contributing factor to the substantial difference in median OS; the OS was 3.9 months longer for patients receiving combination treatment. If the patients overall health state tolerates it, the Dutch guidelines prefers combination treatment as first line therapy. This seems to be in line with the longer OS for the combination treatment group, since younger patients have more often a better overall health state.

Table 6. Treatment costs per treatment group in the outcome research.

Treatment group	Total mean costs	Mean chemotherapy costs	Mean inpatient stay costs
Ineligible	€ 13,899.00	€ 3,672.00	€ 4,455.00
Sequential	€ 19,812.00	€ 7,946.00	€ 6,241.00
Oxaliplatin combination	€ 28,200.00	€ 12,246.00	€ 9,387.00
Irinotecan combination	€ 44,664.00	€ 18,128.00	€ 14,878.00

Inpatient hospital days and chemotherapy were the main cost drivers for the total mean costs. The total mean costs, mean chemotherapy costs and mean inpatient stay costs per treatment group are shown in Table 6.

In the outcome research the results of the eligible patients are compared with the results of the CAIRO trial. The OS was higher in the CAIRO trial than in the outcome research. Patients with combination treatment had a median OS of 15.9 months in the CAIRO trial and 15.1 months in the outcome research. For patients receiving sequential treatment the difference was even bigger; 2.2 months (13.4 vs. 11.2 months). Both the non-random assignment in the outcome research population and the higher motivation to treat in trials than in daily practice can explain the differences in OS.

3.2.6 Conclusions

The outcome research used a retrospective study design to assess the appropriate use and cost-effectiveness of oxaliplatin.

The outcome research had a high percentage of missing values (41% for eligible and 62% for ineligible patients) due to the fact that patients' performance status was not routinely documented by physicians. The performance state of the combination group was significantly better than the performance state of the sequential treatment group. Patients with worse performance state are less likely to receive a more aggressive chemotherapy. The CAIRO eligibility criteria exclude patients with severe comorbidities and the worst performance status. This can explain why 40% of the patients in the ineligible group had a WHO state 3, compared to only 8% of the patients in the eligible group.

The overall mean utility was comparable for sequential and combination treatment (0.77 vs. 0.76, $p = 0.26$). The costs significantly differ between the different treatment groups (Mann-Whitney U-test: $p = 0.014$); substantial variance was found within the treatment groups and in each individual cost component.

The outcome research concluded that upfront combination treatment did not result in a significant overall survival benefit compared to sequential treatment, but that it was more important that patients were exposed to the different chemotherapies during their treatment.

3.3 Dutch daily practice versus clinical trials

3.3.1 Clinical trials

Clinical trials are performed under controlled conditions, but in daily practice conditions will deviate. As a result a clinical trial based determination of cost-effectiveness will not always be the best representation of daily practice. Randomised clinical trials are seen as the best scientific basis for efficacy studies, but the Dutch policy regulation of expensive medication also demands that outcomes research is done. Outcome research is the collection and analysis of data obtained from daily clinical practice, to assess the cost-effectiveness of expensive hospital drugs.²⁰ Due to the increase in incidence, treatment options and median OS, the economic burden of mCRC is expected to increase in the next decade. Therefore cost-effectiveness studies will become more important.

3.3.2 CAIRO versus Outcome research

The baseline characteristics of the patient populations of both CAIRO trial and outcome research are shown in table 7.

Table 7. Baseline characteristics of CAIRO trial and Outcome research.

	CAIRO trail		Outcome Research	
	sequential treatment	combination treatment	sequential treatment	combination treatment
Age - yr				
Median	64	63	64	59
Range	27 - 82	31 - 81	30 - 92	29 - 81
>70	23%	81%	32%	13%
Gender				
Male	63%	63%	58%	62%
Female	37%	37%	42%	38%
Performance status				
PS 0 - 1	95%	96%	47%	53%
PS 2 - 3	5%	4%	13%	6%
Unknown	-	-	40%	41%
Predominant location of metastases				
Liver	69%	71%	84%	81%
Extrahepatic	29%	29%	8%	7%
Unknown	2%	<1%	8%	12%
LDH at randomisation				
Normal	64%	64%	39%	47%
Abnormal	36%	36%	42%	38%
Unknown	-	-	19%	15%
Site of primary tumour				
Colon	63%	57%	67%	59%
Rectosigmoid	7%	8%	10%	12%
Rectum	30%	35%	23%	29%

Patients receiving sequential treatment in first line treatment included in the CAIRO trial were significantly younger ($p = 0.0002$) than patients in the outcome research population. Patients receiving combination treatment in the CAIRO trial were significantly older ($p = 0.0258$) than patients in the outcome research population. Patients in the outcome research population are non-random assigned to their treatment, which can explain this. When the age of patients get higher, the health status mostly decrease. Therefore it is less likely that older patients are assigned to a more aggressive combination treatment than younger patients.

The median OS of the eligible patients receiving sequential treatment was 13.4 months in the CAIRO trial and 11.2 months in the outcome research. The median OS of eligible patients receiving combination treatment was 15.9 months in the CAIRO trial and 15.1 months in the outcome research.

There were three possible causes that patients in trials had better outcomes on primary and secondary efficacy measures than patients in daily practice. First, it seems that there was a higher motivation for treatment of the trial-population; outcome research patients receiving sequential treatment were significantly less often treated with third line therapy than patients in the CAIRO sequential treatment arm.

Second, the patient's health status is generally better in trials, because of the inclusion criteria. And third, in trials physicians have to stick to tight protocols for treating their patients; resulting in more dedication to therapy by physicians.

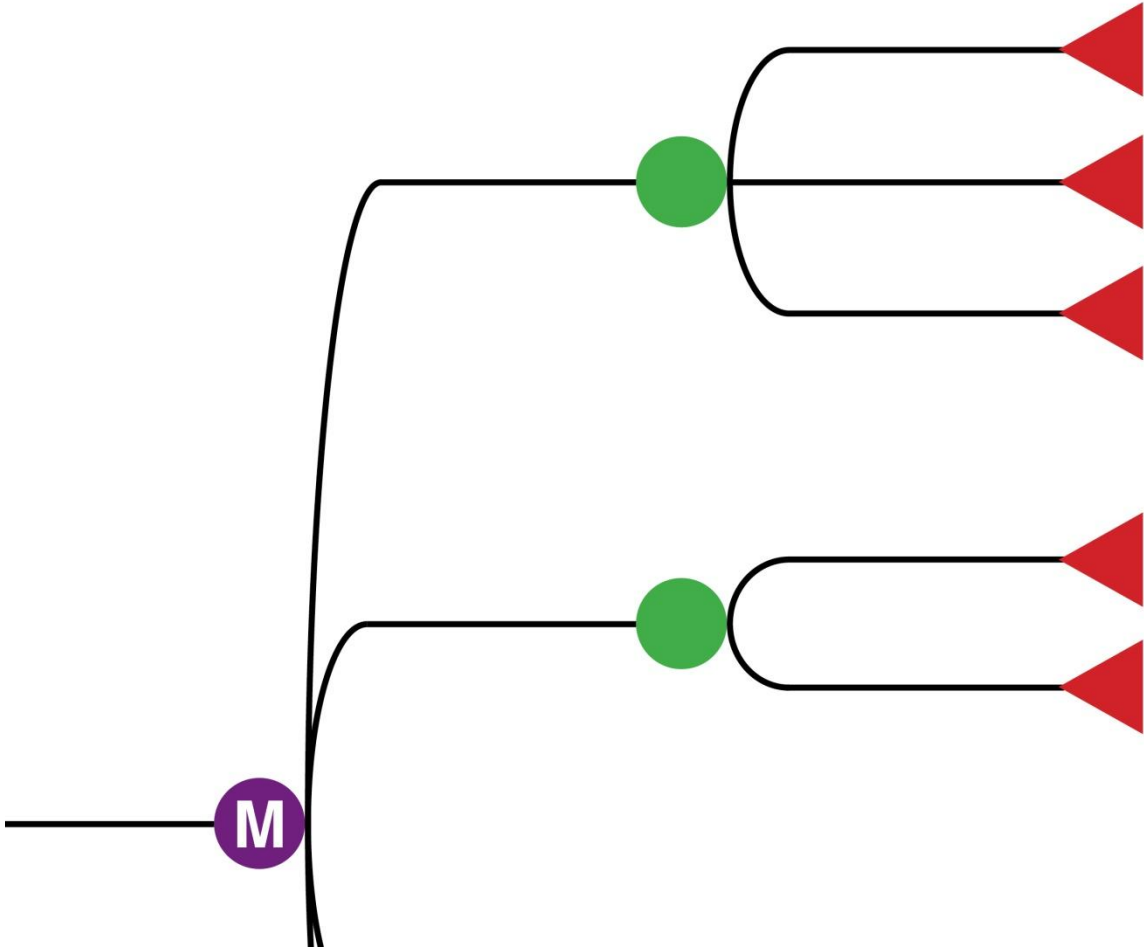
3.3.3 Quality of life

Literature has indicated considerable variability in HRQoL depending on a number of factors, such as treatment stage, side effects and treatment group. The utility scores for the health-state of "cancer" in general, were reported to range from 0.7 to 0.92.²³ The National Institute for Health and Clinical Excellence (NICE) recommended using a standardized and validated generic instrument to quantify the HRQoL.²⁴ No studies have been found that conducted an evaluation on utility values in PFS and progression states, therefore it is possible that a generic instrument may not be able to distinguish the utility of PFS and progression.

In the CAIRO trial the disease specific QoL was measured using the QLQ-C30 questionnaire of the European Organization for Research and Treatment of Cancer (EORTC). The HRQoL was measured before randomisation and every 9 weeks thereafter. Regression coefficients have been used to transition the HRQoL results of the QLQ-C30 into health utility values. The regression coefficients are:

$$\begin{aligned} \text{EQ-5D index (Dutch tariff)} = & 0.985 + (1^*-.037) + (2^*-.025) + (3^*-.059) + \\ & (4^*-.033) + (5^*-.134) + (6_level2^*-.033) + (6_level3^*-.067) + \\ & (6_level4^*-.180) + (7_level2^*-.013) + (7_level3^*-.037) + \\ & (7_level4^*-.012) + (9_level2^*-.065) + (9_level3^*-.053) + \\ & (9_level4^*-.189) + (16_level2^*-.038) + (16_level3^*-.045) + \\ & (16_level4^*-.126) + (23_level2^*-.028) + (23_level3^*-.049) + \\ & (23_level4^*-.456) + (24_level2^*-.053) + (24_level3^*-.140) + \\ & (24_level4^*-.232) + (27_level2^*-.027) + (27_level3^*-.091) + \\ & (27_level4^*-.110) . \end{aligned}$$

4 Methods



4.1 Objective

The incidence of mCRC is still rising and partly for this reason the prediction is that more than 14,000 people will be diagnosed with colorectal cancer in 2015.²⁵ In the last two decades many new treatments became available and the life expectancy of mCRC patients almost quadrupled to around two years. Both new treatments and an increase in OS will raise the expenditure on treatment for mCRC. The healthcare system has a main resource limitation; the financial incentive to keep the system affordable for the society. Therefore cost-effectiveness analysis is important.

This thesis has two endpoints; Costs per life-year (LY) gained and costs per quality adjusted life-year (QALY) gained.

The incremental costs per LY gained has been calculated for the cost-effectiveness analysis (CEA). The incremental costs per QALY has been calculated for the cost-utility analysis (CUA). The CUA is the main techniques used to compare costs and health utility values of competing healthcare interventions.

The cost-effectiveness model was build using data from the oxaliplatin outcome research. Since data was collected retrospectively in 2008 and 2009 about the years 2003 and 2004, there were limitations to the available data. For example it was impossible to collect all the information on societal costs. Some of the data that was not available in the outcome research was abstracted from the CAIRO trial. The source of the data will be mentioned when the data are discussed.

This economic evaluation uses the hospital perspective instead of the common used societal perspective. The hospital perspective is a health care sector perspective that is limited to hospital activities. Societal costs and costs the patient made were ignored in the hospital perspective; the productivity costs and costs of informal care were not taken into account. Most patients with mCRC were near or beyond retirement age, which make the expected productivity losses very small. It can be expected that both informal care and productivity costs would not differ for different treatments, but increases total costs for both approximately equally.

The primary objective of this thesis was to assess the real-world cost-effectiveness ratio of combination versus sequential chemotherapy in the treatment of mCRC patient that are not eligible for curative treatment.

4.2 Model

4.2.1 Model overview

The outcome research population reflects the population of patient diagnosed with mCRC that received sequential or combination treatment in 2003 and 2004. Demographics and baseline characteristics need to be similar between the two therapy groups to create a proper comparison. Both the sequential and the combination treatment group contain eligible and ineligible patients. The percentage of ineligible patients was 38.8 for the sequential treatment group and 25.8 for the combination treatment group.

Since the ineligible patients are a main part of the daily-practice patient population they were included in the treatment groups. This made it possible to base the model on more patient level data, than when the ineligible patients were excluded from the population. It is not possible to compare eligible and ineligible patients with each other. By including the ineligible patients in both the sequential and the combination treatment group, no direct comparison need to be made between eligible and ineligible patients. The comparison was made between two treatment groups, both containing eligible and ineligible patients.

Demographic and baseline clinical characteristics of the sequential and the combination group show differences in age distribution and WHO performance status. No correction will be made for these differences, as the objective is to represent the daily practice and the choice for either sequential or combination treatment is related to the patient's age and overall health status.

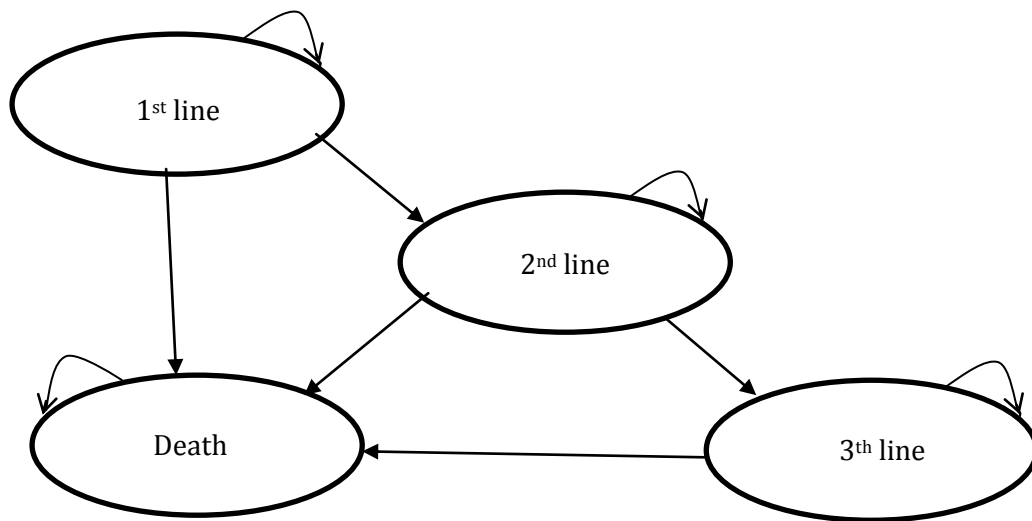
For the treatment of mCRC four regimens were used in Dutch daily practice (see Table 1). All treatments were administered until disease progression, the occurrence of toxicity level 3 or higher, other serious adverse events (SAEs), death or finishing the predetermined set of cycles which was followed by a treatment-free interval.¹³

The endpoints used in this thesis were the incremental cost per life-year gained and the incremental cost per QALY gained. Direct medical costs such as drug costs, drug administration costs, costs for the treatment of AE's and follow-up costs were included. The health benefits measure used was life-years gained and QALYs gained. The two survival components were PFS and OS, the patient level data of both were derived from the outcome research. The QoL component and cost data were derived from the outcome research. The cost per LYG and QALY gained is presented over a lifetime horizon and costs were discounted at 4% and effects were discounted at 1.5%.

4.2.2 Model structure

The model in the CEA is shown in Figure 5, this model is based on a the model developed by Pandor et al, which is shown in appendix F Figure 1. The development of the model has also been visualised in appendix F. The model contains four states; 1st line treatment, 2nd line treatment, 3th line treatment and death.

Figure 5. Conceptual model.



A Markov model was developed to simulate the transition of patients receiving treatment for mCRC through clinical states that are typically observed in a setting. Each state is mutually exclusive, thus a patient could only be in one state at any one time.

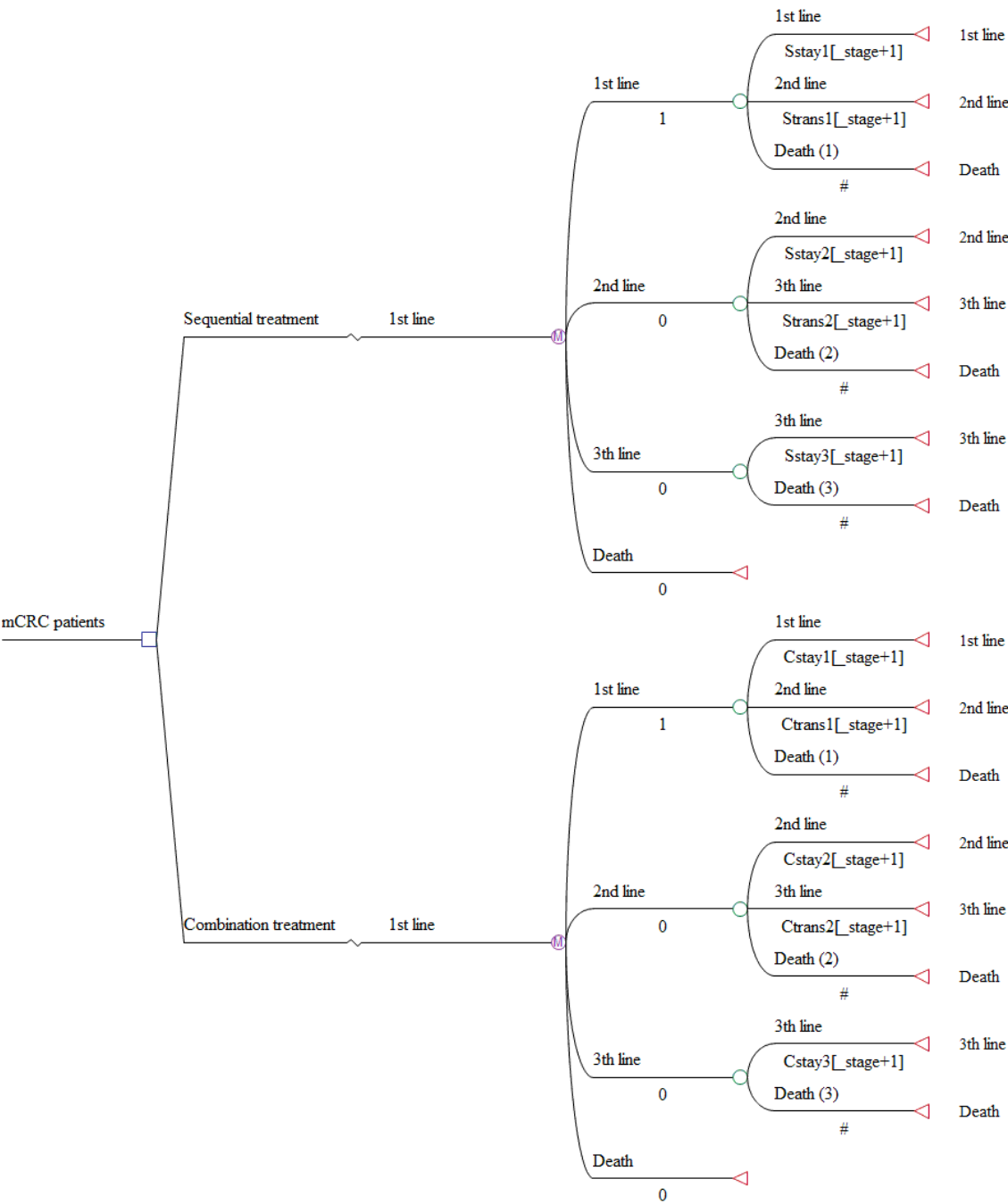
Specific key model features are listed below:

1. Patients could be in only one of the four states at any point in time; 1st line treatment, 2nd line treatment, 3th line treatment or death.
2. All patients start in the 1st line treatment state.
3. Patients who are in 1st line treatment in the current cycle, could remain in 1st line treatment, or could transition either to the 2nd line treatment or death in the next cycle.
4. Patients who are in 2nd line treatment in the current cycle, could remain in 2nd line treatment, or could transition either to the 3th line treatment or death in the next cycle.
5. Patients who are in 3th line treatment in the current cycle, could remain in 3th line treatment or could transition to death in the next cycle.
6. Each treatment line starts at the first day of that treatment line and stops the day before a new treatment line starts or the patient transfer to death; if a patient has a treatment-free interval, the interval is included in the previous treatment line.
7. Each cycle lasts for 90 days
8. The Markov process stops after 20 cycles.
9. The incremental cost per life-year gained and per QALY gained was calculated.

The Markov model structure of Pandor et al. has been used within other appraisals of oncology therapy.²² In addition, the model design was reviewed and approved by an international panel of experts. The model was believed to be a reasonable simplification of the disease process. The model structure has been further validated with expert interviews conducted by Abacus International, the original developers of the model.²⁶

The Markov model is shown in the form of a decision tree in Figure 6.

Figure 6. Markov model structure.

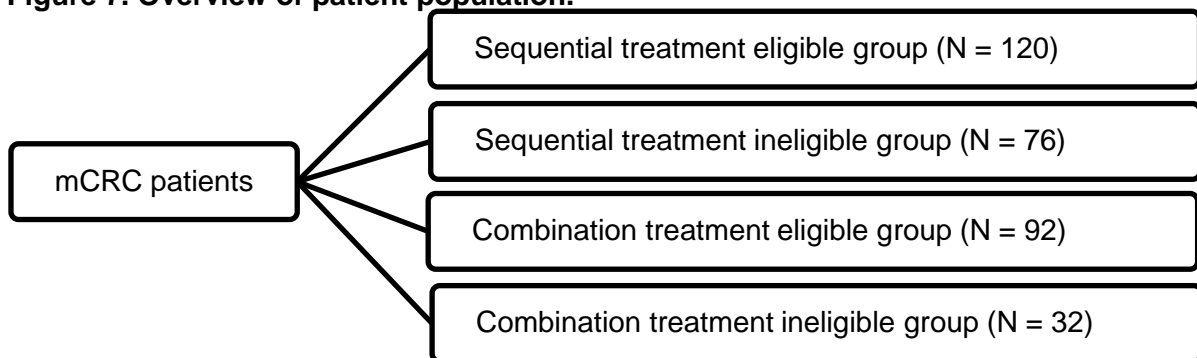


4.3 Input parameters

4.3.1 Patient population

The patient population used in the cost-effectiveness model includes data from 320 patients and is shown in Figure 7. This patient population was selected from the 433 medical files that were reviewed in the outcome research. Patients were selected using the inclusion and exclusion criteria of the CAIRO trial, which were similar to the criteria used in the outcome research. Two main exceptions are been made in the selection for this thesis' patient population; patients that did not receive sequential or combination treatment in the standard order are not excluded (they are mentioned below) and patients that were included in another trial but only received capecitabine, oxaliplatin and irinotecan are also not excluded. Seven of the patients were not evaluable on eligibility and were therefore excluded. This resulted in 320 patients in this thesis' patient population.

Figure 7. Overview of patient population.



The patient population was the input for this thesis' model. The baseline characteristics were analysed for two reasons; to compare the input data with the data of the outcome research and to make comparison possible between the input and the output of this thesis' model. The characteristics are listed below per treatment group.

Sequential treatment

In first line sequential treatment 97.5% of the eligible patients received monotherapy. Oxaliplatin combination treatment was received by 0.8% of all patients and irinotecan combination treatment was received by 1.7% of all patients. Of the ineligible patients 93.4% received mono-, 5.3% received irinotecan and 1.3% received oxaliplatin combination treatment. In second line 51.3% of the eligible and 6.7% of the ineligible patients received monotherapy. Of the eligible patients 5.3% received oxaliplatin combination treatment compared to 50% of the ineligible patients. Irinotecan combination treatment was received by 42.1% of the eligible and 43.3% of the ineligible patients. One eligible patient received combination treatment with both oxaliplatin and irinotecan in second line treatment. In third line 58.1% of the eligible patients received monotherapy, 3.1% received oxaliplatin combination treatment and 38.7% received irinotecan combination treatment.

Two of the sequential patients started with a treatment of either irinotecan or oxaliplatin where 5-FU/LV is standard. These patients then receive 5-FU/LV monotherapy in second

line treatment. Both patients did not die before third line treatment and are therefore not excluded.

The median OS was 9.9 months compared to 11.2 months in the outcome research, and 16.3 months in the CAIRO trial. The median OS of the model is therefore expected to be lower than the OS of the CAIRO trial.

Combination treatment

Some of the patients in combination treatment receive a third line treatment; 26 patients in total. These patients receive an extra line of oxaliplatin or irinotecan combination treatment or a combination treatment with both oxaliplatin and irinotecan (irox combination), six patients received FL monotherapy.

In first line treatment 83.7% of the ineligible and 71.9% of the eligible patients received an oxaliplatin containing combination regimen. Of the eligible patients 18.8% received irinotecan combination treatment compared to 16.3% of the ineligible patients. Three of the eligible patients received a combination treatment of both irinotecan and oxaliplatin in first line. In second line treatment 62.5% of the eligible patients received irinotecan and 25.0% received oxaliplatin. Six point three percent of the eligible patients received both irinotecan and oxaliplatin during their different treatment lines. This compared to 12.1 and 6.9 percent of the ineligible patients. Of the ineligible patients in third line treatment 22.7% received irinotecan and 36.4% received oxaliplatin. Irox combination treatment was given to 75% of the eligible and 18.2% of the ineligible patients. One of the eligible and five of the ineligible patients received FL monotherapy in third line treatment.

The median OS was 16.4 months, compared to a median OS of 15.1 months in the outcome research. This OS was lower the median OS of the CAIRO trial and higher than the median OS of the outcome research. When ineligible patients were excluded from the patient population the median OS was still in between the other trials. The expectation is that the outcomes of the model will also be a bit higher than the OS the outcome research.

4.3.2 Transition probabilities

4.3.2.1 Model transition probabilities

The following nine transition probabilities were used in this thesis;

1. Probability of staying in 1st line treatment
2. Probability of transitioning from 1st line treatment to 2nd line treatment
3. Probability of transitioning from 1st line treatment to death
4. Probability of staying in 2nd line treatment
5. Probability of transitioning from 2nd line treatment to 3th line treatment
6. Probability of transitioning from 2nd line treatment to death
7. Probability of staying in 3th line treatment
8. Probability of transitioning from 3th line treatment to death
9. Probability of staying in death

The transition probabilities are time dependent variables in which transitions takes place every three months. Patients in the 1st line treatment state may either stay in that state [P(stay 1)], transition to the 2nd line treatment [P(transition 1)], or die [P(death 1)]. These transition probabilities were obtained from Kaplan-Meier curves (probabilities a-c in Table 8).

Table 8. Summary of model transition probabilities.

Key Probabilities	Sources
a) Probability of stay in line 1 [P(stay 1)]	Stay in first line Kaplan-Meier curve with event defined as stay 1 (Appendix G1 / H1)
b) Probability of transition from line 1 to line 2 [P(transition 1)]	Time to transition Kaplan-Meier curve with event defined as transition 1 (Appendix G2 / H2)
c) Probability of transition from line 1 to death [P(death 1)]	$1 - P(\text{stay 1}) - P(\text{transition 1})$
d) Probability of stay in line 2 [P(stay 2)]	Stay in second line Kaplan-Meier curve with event defined as stay 2 (Appendix G3 / H3)
e) Probability of transition from line 2 to line 3 [P(transition 2)]	Time to transition Kaplan-Meier curve with event defined as transition 2 (Appendix G4 / H4)
f) Probability to transition from line 2 to death [P(death 2)]	$1 - P(\text{stay 2}) - P(\text{transition 2})$
g) Probability of stay in line 3 [P(stay line 3)]	Stay in third line Kaplan-Meier curve with event defined as stay 3 (Appendix G5 / H5))
h) Probability of transition from line 3 to death [P(death 3)]	$1 - P(\text{stay 3})$
i) Probability of stay in death [P(stay death)]	Probability is 1

4.3.2.2 Cumulative survival data

Appendix I shows the cumulative proportions of stay in current treatment line, transition to the next treatment line or transition to death as derived directly from the Kaplan-Meier curves. These proportions have to be converted into transition probabilities before they can be used in the Markov Model.

4.3.2.3 Transition probabilities

The transition probabilities were calculated from the proportion Kaplan-Meier curves with the use of the formulas as depicted by Briggs et al.²⁷ The transition probabilities of stay in the current treatment line, transition to the next treatment line or transition to death as used in the model are shown in appendix J.

Probability of stay in the current treatment line

The cumulative data of stay in current treatment line were converted to transition probabilities for stay using the following formula:

$$P(\text{stay } t) = \frac{P_t}{P_{t-1}}$$

Where P_t and P_{t-1} denote the cumulative probability of stay at the end of time t and $t-1$, respectively; $P(\text{stay } t)$ denotes the transition probability for time t .

Probability of transition to the next treatment line

The cumulative data of transition to the next treatment line were converted to transition probabilities for dying using the following formula:

$$P(\text{transition } t) = \frac{(P_t - P_{t-1})}{1 - P_{t-1}}$$

Where P_t and P_{t-1} denote the cumulative probability of transition at the end of time t and $t-1$, respectively; $P(\text{transition } t)$ denotes the transition probability for time t .

Probability of transition to death

The probability of transition to death was calculated using the following formula:

$$\text{Prob}(\text{die } t) = 1 - \text{Prob}(\text{stay } t) - \text{Prob}(\text{transition } t)$$

Where t denote the number of the current treatment line.

4.3.3 Utility parameters

Patients' utility was derived from the QLQ-C30 responses as collected in the CAIRO trial.

The retrospective study design of the outcome research made it impossible to collect HRQoL data. As said before both the CAIRO trial and the outcome research were done in the same source population. Therefore the disease specific QoL data are taken from de CAIRO trial, since this was the second best option.

The QLQ-C30 mapping model was used to produce health utilities from the HRQoL. This mapping model has been developed using data on multiple myeloma. This model has also been validated in non-Hodgkin cancer.²² The model provides stable outcomes on haematological cancers and therefore no problems are expected to occur in the use for colorectal cancer.

In the CAIRO trial there was only one significant difference in QoL outcomes; diarrhoea less occurred in sequential treatment than in combination treatment

The health utilities as used in this theses are shown in Table 9 and have been used to calculate costs per QALYs, rather than costs per life-year only.

Table 9. Health utility values.

	Sequential therapy			Combination therapy			
	Mean	sd	N	Mean	sd	N	
Baseline	0,76	± 0,20	385	0,75	± 0,22	362	<i>P-value</i>
WK 9	0,76	± 0,21	208	0,74	± 0,22	199	
Wk 18	0,79	± 0,18	188	0,74	± 0,20	194	
WK 27	0,81	± 0,17	149	0,80	± 0,15	135	
WK 36	0,75	± 0,22	132	0,75	± 0,24	102	
WK 45	0,78	± 0,22	105	0,76	± 0,21	84	
WK 54	0,78	± 0,17	98	0,76	± 0,17	76	
WK 63	0,76	± 0,19	68	0,77	± 0,19	58	
WK 72	0,77	± 0,18	61	0,82	± 0,15	49	
WK 81	0,75	± 0,22	33	0,83	± 0,12	33	
WK 90	0,71	± 0,21	32	0,76	± 0,16	30	
WK 99	0,73	± 0,20	27	0,81	± 0,22	19	
WK 108	0,80	± 0,22	15	0,89	± 0,10	8	
Totals	0,77	0,20	1501	0,76	0,20	1349	

Source: Van Gils 2010

4.4 Cost input

Cost data were extracted from the outcome research. In the outcome research chemotherapy and inpatient hospital days were the most important cost drivers. Due to the data collection method it was not possible to extract inpatient stay costs as a variable for each treatment line separately. Therefore weighted averages of the total other costs were calculated for each treatment line. Costs were divided in total other costs, medication costs and costs related to end of life care.

In the outcome research the costs were calculated by multiplying the resources used with the unit costs; first the used resources and unit costs for individual patients are determined, afterwards the total costs per patients are calculated. The included costs in this thesis were the same as the costs included in the outcome research, because the costs in this thesis were abstracted from the outcome research.

The following types of resources were collected: hospitalization for chemotherapy or adverse events, chemotherapy drug costs, concomitant medications, medical devices, and patients' travel expenses. Intensive care days, emergency room visits, radiological procedures and laboratory services were in the outcome research assumed to be identical for different treatment options and therefore not included in the cost analysis. Since the cost data of total other costs was taken from the outcome research these four elements were also not included in this thesis.

4.4.1 Chemotherapy costs

The costs of chemotherapy were included in the model per cycle, per treatment line and per used chemotherapy.

Wastage, the remaining amount of medication which was left in the vial if the volume was not the same as the administered dosage, was not included in the calculation. This because the used chemotherapeutic agents are standard and can therefore be used for other patients.

The CVZ has provided the unit costs of chemotherapy.²⁸ Cost of 2009 were used, because of the comparison with the outcome research. To calculate the medication costs standard planned doses were used. Medication was administered in cycles of 3 weeks; 21 days. The unit costs per dosage and planned dosages are showed in appendix K. These Tables were used to calculated the medication costs; the planned dosage is multiplied by the average body surface and the unit costs of the administered medication. The used average body surface was 1.79, this was abstracted from the UK survey of Sacco, et al.²⁹

The costs were transitioned into costs per chemotherapy per cycle of 90 days. The costs per chemotherapy are shown in appendix K3 and used to calculate a weighted average per treatment line. For example; in first line combination treatment 80.6% of the patients received oxaliplatin combination treatment, 16.9% received irinotecan combination treatment and 2.4% received irox combination treatment. This gave a weighted average of € 5,897.38 per patient. The weighted averages per cycle as used in the model are shown in Table 10.

Table 10. Weighted averages for different treatment lines per treatment cycle.

Treatment line	Treatment type	
	sequential	combination
1st line	€ 2,627.15	€ 5,897.38
2nd line	€ 4,344.50	€ 5,204.09
3th line	€ 4,253.92	€ 5,005.51

4.4.2 Total other costs

The total other costs were included in the model as initial costs. Initial costs are assigned at the beginning of the first line treatment. Since all patients start in first line treatment all patient receive the same total other costs. Therefore a weighted average was calculated.

The total other costs were all abstracted from the outcome research. Therefore it should be noted that due to the diversity of treatment agents and drugs that were used in daily practice a wide cost variation existed between different patients. There should also be noted that there was limited real-life costs data available; 57 patients receiving first-line monotherapy, 51 patients receiving oxaliplatin combination treatment, 11 patients receiving irinotecan combination treatment and 11 patients that were ineligible (independent of the received therapy type).

The total other costs included; hospitalization for chemotherapy or adverse events, costs for concomitant medications and medical devices, and patients' travel expenses.

4.2.2.1 Resource use

Hospitalization for chemotherapy or adverse events

The hospitalization costs included both hospital admissions and visits to the outpatient clinic. Data was obtained from the patients' maximal CRFs. The number of visits to outpatient clinic also included visits for chemotherapy administration and check-ups.

Only AEs which led to hospitalization were included. In general, expert panels recommended to include grade 2 – 4 AEs. Costs for grade 2 – 4 AEs that are not hospitalized were assumed to be identical for different treatment options and were therefore not included in the cost analysis. In the outcome research cost data of AEs was obtained from the patients' maximal CRFs.

Concomitant medication

Concomitant medication included all medication other than chemotherapy; blood products given to support the chemotherapeutic drugs, medication to reduce symptoms of side effects and medication for the treatment of adverse events.

The use of concomitant medication and corresponding costs widely varies over the different patients. In the outcome research cost data was obtained from the patients' maximum CRFs.

Medical devices and hospital services

Medical devices and hospital services included administration devices for treatment and disposal pumps, but also laboratory tests, radiotherapy and surgery (when applied). In the outcome research cost data was obtained from the patients' maximum CRFs.¹⁹

Patients' travel expenses

In the outcome research zip code and treatment location were obtained of the DCR. Patients' travel distance to the hospital was used to calculate patients' travel expenses. In the outcome research distance was multiplied by a standard fee per kilometre.¹⁹

4.2.2.2 Unit costs

The NZa has standard fees for specific hospital services, these were used to determine the costs of surgical procedures, radiotherapy, laboratory services and medical imaging.³⁰ The oncological specific unit prices are known to be slightly higher compared to the average prices in the Dutch Costing Manual of 2004. Two micro-costing studies of Tan et al. were used to compute the oncological specific unit prices.^{31, 32} Tan also included overhead costs to represent the full hospital costs. There were two origins of the unit costs; general hospitals and university hospitals. Most unit costs are weighted to reflect the distribution of patients among hospitals in Dutch daily practice: 33% from the university hospitals and 67% from the general hospitals. The unit costs for inpatient hospital days, intensive care days, outpatient visits, consulting by telephone, day-care treatment, and emergency room visits are shown with their weighting factor in appendix L.

Cost data was extracted from the outcome research and was divided into 4 subcategories; ineligible patients, monotherapy, oxaliplatin and irinotecan combination treatment. In this thesis we also included ineligible patients in our model, so the costs are converted to ineligible costs per treatment type. The average costs for ineligibles per treatment type has been calculated based on the total mean costs for ineligible patients and the received treatment type, both cost data was abstracted from the outcome research. The total average costs per patients are shown in appendix L.

With regard to irox combination treatment no literature was found about costs. The costs for irox combination treatment were attributed to the most expensive treatment; irinotecan. Costs were not expected to be higher than irinotecan because of the lower dosages of both chemotherapeutic drugs, but were not expect to be lower because the side effects of both irinotecan and oxaliplatin could occur.

4.2.2.3 Weighted average

The weighted average of each treatment type is calculated by weighting the amount of ineligible and eligible patients per treatment type. Next, the weighted average of the both sequential and combination treatment arms have been calculated. The weighted average was € 15,237.56 per patient for combination treatment and € 15,237.56 per patient for sequential treatment.

The total other costs as used in the model are € 11,839.64 for the sequential treatment arm and € 15,237.56 for the combination treatment arm. All patients receive these costs at the start of first treatment line.

4.4.3 Costs related to end of life care

Economic evaluation has been done on palliative care for patients with mCRC. The mean costs related to the end of life care for these patients was approximately £600.³³ First these costs were transferred to costs of 2009 using the U.K. inflation of 2007 and 2008 (both 3%). Then these costs were converted using purchasing power parities (PPPs) of the world data bank. The PPPs of private consumption were used because it has been substantiated by a bigger dataset than the PPPs for medication. The costs related to end of life care as used in this model were € 556.97 per patient.

4.5 Model assumptions

Because of the limitations or gaps in the current literature, certain assumptions were made to simplify the Markov model, yet to best reflect the clinical practice. The clinical assumptions critical to the modelling approach are listed below:

1. A patient could only be in one of the four states in a particular cycle.
2. A constant utility value was assumed for an overall mCRC condition regardless of treatment, health status and time points.
3. It was assumed that all AEs that not resulted in hospitalization were not significant.
4. AEs were viewed as independent events; no relationship among the AEs was assumed.
5. The average life expectancy after 5 years is equal for all treatment alternatives.

4.5.1 Time horizon and discounting

The time horizon of the Markov model for mCRC was limited to 5 years. It was assumed that the probability of transition from treatment line 3 to death after 5 years is equal in the whole target population. This assumption has often been used in the past.³⁴ Implementation of remaining life expectancies for state 3 patients into the model made it possible to model costs and benefits over a lifetime horizon.

Cost and benefits incurred after the first year in the model were discounted at 4% and 1.5% per annum respectively, consistent with current Dutch guidelines.³⁵ Costs were expressed in Euro's for the year 2009.

4.5.2 Base case analyses

For this model incremental CEA were conducted. Costs were abstracted from the outcome research or otherwise from the CVZ. Medication costs were calculated for each treatment state for both sequential and combination treatment and total other costs were estimated for each state over the time horizon of the model. Survival was calculated for all patients in each state of the cycle for both treatment arms. Utility values were abstracted from the CAIRO trial and were summed from each cycle to determine the total number of QALYs gained.

The incremental cost-effectiveness ratio (ICER) is the ratio of the difference in total costs to the difference in total QALYs per treatment arm.

Half-cycle correction can be used to correct for patients that transfer or die during the cycle, because the costs are assigned to the patients at the beginning of the cycle. Initial costs were only assigned in first line treatment and were weighted averages. The incremental costs were also based on weighted averages. The weighted averages took patients' survival already into account, which made it unnecessary to apply half-cycle correction. The final costs were assigned to the patients that die. Half-cycle correction was not applicable for the costs related to end of life care, because these costs were assigned at the end of the cycle.

4.6 Statistical analyses

Different sensitivity analyses have been conducted to test the robustness of the model as designed in this thesis.^{36, 37}

4.6.1 One-way sensitivity analyses

A univariate or one-way sensitivity analyses (OSA) has been performed to exam the sensitivity of the model outcomes to the varying levels of one parameter.³⁸ The OSA was shown in a tornado-diagram.

While conducting an OSA only one parameter was varied when other parameters were hold at their base case value. Therefore the impact of a single parameter could be observed. The OSA for utilities and costs were shown in a tornado-diagram that reflects the ICERs per QALY gained.

The OSA on transition probabilities was done by shifting the Kaplan-Meier curve up- and downwards. Therefore the HR were varied. The HR from the sequential to the combination treatment was abstracted from the CAIRO trial. For every cycle the transition probabilities were recalculated. The limits were calculated using the following formulas:

$$HR_{\text{lower}} = HR * 1.08$$

$$HR_{\text{upper}} = HR * 0.79$$

Were HR denotes the HR from the original Kaplan-Meier curves.

Only the HR of the P(stay) was adjusted, P(stay) was then recalculated using the same formula as used in the deterministic model. P(transition) was held equal. P(die) had to be recalculated since the formula include P(stay). P(die) was recalculated using the same formula as used in the deterministic model.

4.6.2 Probability sensitivity analyses

Probability sensitivity analyses (PSA) has been performed to check the robustness of the deterministic model. It can identify sources of uncertainty and can help deal with these uncertainties.³⁹

By conducting a PSA, reasonable changes in the models parameters could be made simultaneously to several variables. Changes in costs, effects and transition probability were made at the same time to see if a change in the optimal strategy of the model occurred. The PSA has been performed using a two dimensional Monte Carlo simulation. Second order parameters were selected from the distributions. Then 10,000 iterations were performed. A willingness-to-pay threshold (WTP) of € 50,000 per QALY gained was used, as this was a common used threshold in pharmaceutical funding decisions.⁴⁰

Transition probability parameter distributions

In the PSA the beta distribution was used to represent the uncertainty in the estimated transition probability. The beta distribution was based on two parameters; α and β . The alpha and beta was calculated using the following formulas:

$$\alpha = r$$

$$\beta = n - r$$

Where r denotes the number of events; n denotes the sample size.²⁵

The alphas and betas were extract from the survival tables of the Kaplan-Meier curves (Appendix G for sequential and H for combination treatment).

Unit cost parameters

The triangular distribution was chosen to represent the variation in costs and was based on three parameters; the minimum, the likeliest and the maximum.

The chemotherapy costs and the total other costs were varied 30% to calculate the minimum and maximum bound. These bounds were used to run the sensitivity analyses. No sensitivity analyses was run on cost related to end of life care; since this was considered to be stable.

Utility values

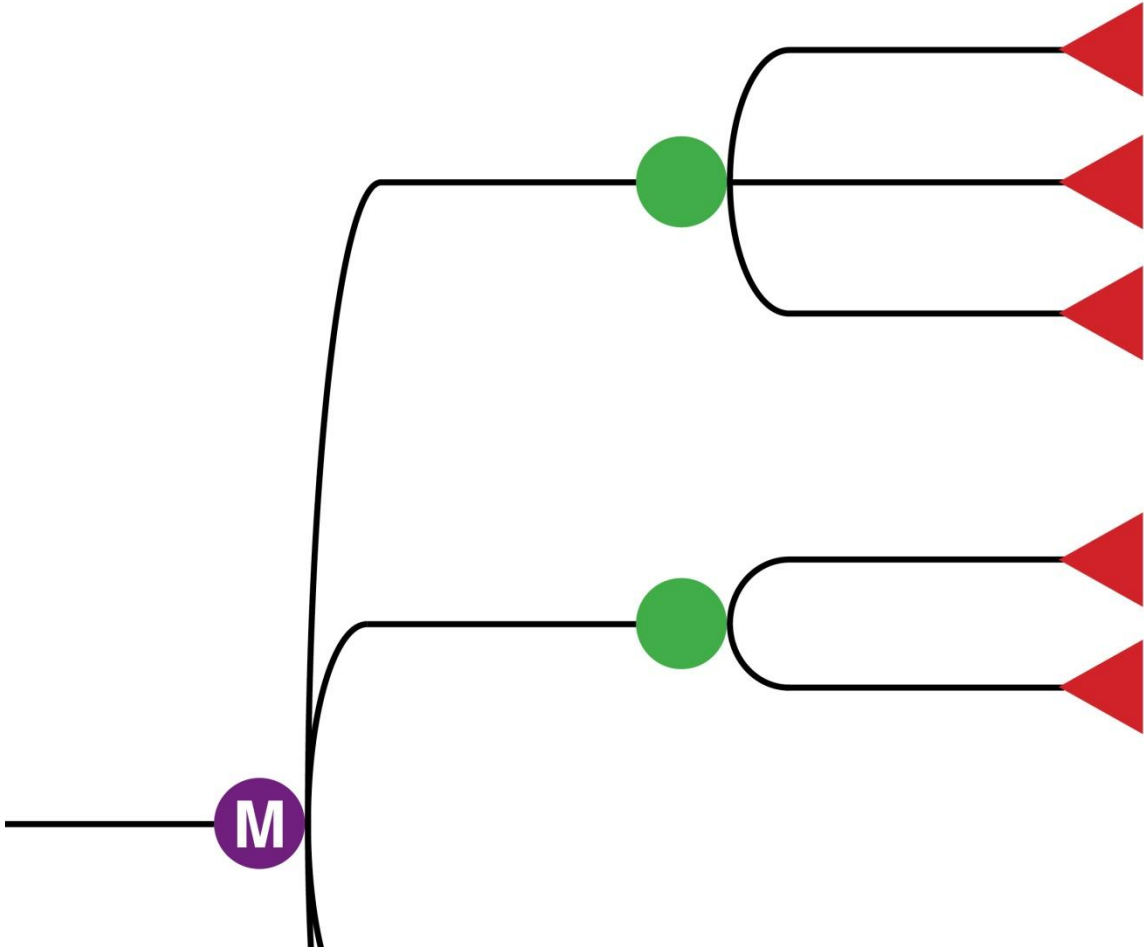
A beta distribution has been used to represent the uncertainty in the utility values. The α and β were calculated based on the mean and standard deviation of the utilities, abstracted from the outcome research. The following formulas were used to calculate the α and β :

$$\alpha = \bar{x} \left(\frac{\bar{x}(1 - \bar{x})}{v} - 1 \right)$$
$$\beta = (1 - \bar{x}) \left(\frac{\bar{x}(1 - \bar{x})}{v} - 1 \right)$$

4.6.3 Discounting

The cost-effectiveness of the deterministic model (with discounting) was compared to the undiscounted model. A zero-discount rate has been used in a two-way sensitivity analyses to show the effect of discounting. The zero-discount rate was used for both costs and effects. The model was run for both life-years and QALYs, for both a comparison has been made.

5 Results



5.1 Model results

The input for the model of this thesis was patient level data from the CAIRO trial and data abstracted from the outcome research. The input and output data from the deterministic model were compared by face validity (input and output graphs are shown in appendix M and appendix N). Comparison showed similar outcomes; the average OS in the sequential treatment arm was 11.2 months in the model's output and 13.3 months in the model's input, the average OS in the combination treatment was 19.1 months in the model's output and 19.7 months in the model's input.

Table 11 shows the costs and effects, in both LYs and QALYs gained, for both treatment arms. The combination treatment arm was the most expensive and most effective treatment arm; € 26,022 more for an average of 7.9 months longer OS or 0.53 QALYs more.

The ICER of combination compared to sequential treatment was € 49,172 per QALY gained and € 39,373 per LY gained.

Table 11. Output of deterministic model.

	Treatment type	Effects	Costs	ICER
Life Years	Sequential	0.93	€ 24,336	€ 39,373
	Combination	1.59	€ 50,358	
QALYs	Sequential	0.72	€ 24,336	€ 49,172
	Combination	1.25	€ 50,358	

Table 11 shows that, with combination treatment more LY and QALYs are gained than with sequential treatment, but this gain comes with an increase in costs. The ICER for combination over sequential treatment did not exceed the upper WTP limit of € 50,000 per QALY gained, but the ICER reached this limit closely.

5.2 Statistical analyses

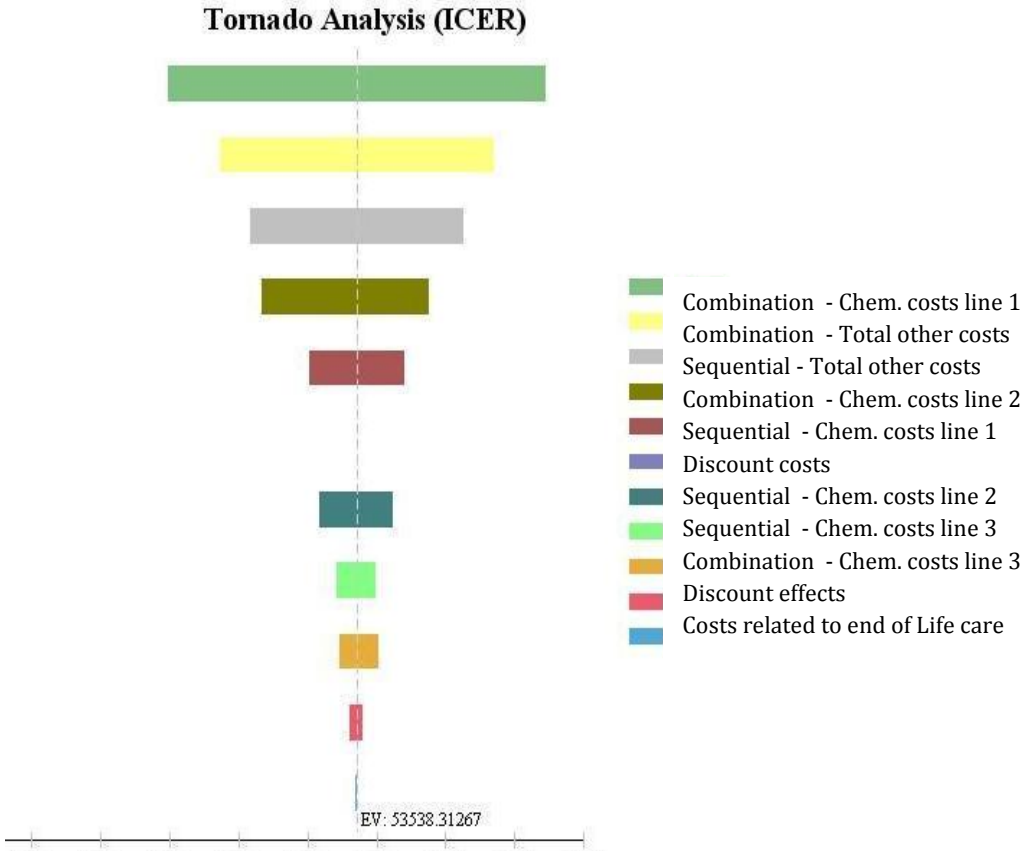
5.2.1 One-way sensitivity analyses

OSA is shown in a tornado-diagram and an additional regression is done on the transition probabilities.

Figure 8 show the tornado diagram used to exam the sensitivity of the model outcomes to the varying levels of one parameter.

The variable were arranged in descending sequence of influence that the parameters had on the ICER.

Figure 8. Tornado diagram showing most influential variable on the ICER per QALY gained.



While conducting an OSA only one parameter was varied when other parameters were hold at their base case value. Therefore the impact of a single parameter could be observed. The parameters were varied with 30%. The most influential variable was the chemotherapeutic costs of first line combination treatment, which makes the ICER vary € 27,386 per QALY (from € 39,845 to € 67,231 per QALY).

The cost of a first line treatment was expected to be more influential than the costs of second line treatment, and second line treatment was expected to be more influential than third line treatment. More patients were in earlier treatment lines so costs were multiplied by more patients. This expectation seems to be true as can be seen in Figure 8.

The parameters that created a variation between € 10,000 and € 20,000 per QALY were:

- Other treatment costs of combination treatment (vary from € 43,597 to € 63,479)
- Other treatment costs of sequential treatment (vary from € 46,660 to € 61,262)
- Chemotherapeutic costs of second line combination treatment (vary from € 45,814 to € 58,810)

The parameters that created a variation between € 5,000 and € 10,000 per QALY were:

- Chemotherapeutic costs of first line sequential treatment (vary from € 50,093 to € 56,983)
- The discount rate for costs (vary from € 16,438 to € 22,078)
- Chemotherapeutic costs of second line sequential treatment (vary from € 50,866 to € 56,210)

Table 12. Outcomes of the OSA on transition probabilities.

Treatment		Effects (QALY)	Costs	ICER (per QALY)
Sequential	Original	1.25	€ 50,358	€ 40,155
Combination over sequential				
Combination	Lower	0.20	€ 21,514	€ 5,345
	Higher	2.80	€ 192,079	€ 68,517
Sequential over combination				
Combination over sequential				

Figure 9. ICERs of combination over sequential treatment.

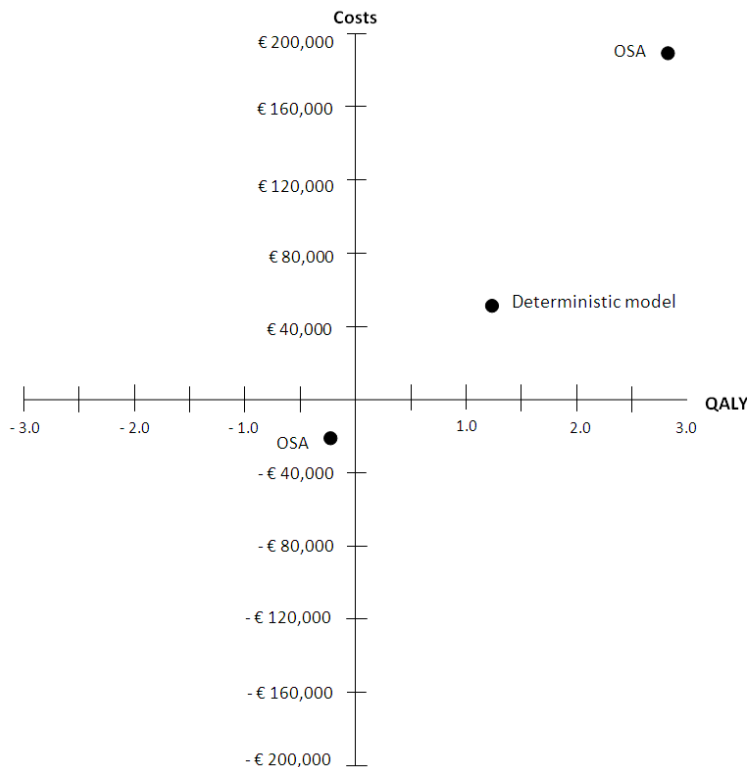


Table 12 shows the output of the OSA on the transition probabilities. The outcomes were as expected. The lower Kaplan-Meier curves, from the higher hazard-ratio, resulted in an ICER of € 5,345 per QALY of sequential over combination treatment. As shown in the lower left quadrant of Figure 9, sequential treatment was cheaper and had better results than combination treatment. The higher Kaplan-Meier curves, from the lower hazard-ratio, resulted in an ICER of € 68,517 per QALY for combination over sequential treatment. This was shown in the upper right quadrant of Figure 9, which also contains the ICER of € 40,155 per QALY for combination over sequential treatment for the original Kaplan-Meier. The ICERs in the upper right quadrant show more QALYs gained for combination over sequential treatment, but also for higher costs.

5.2.2 Probability sensitivity analyses

Table 13 show the average of 10,000 iterations per QALY performed for the PSA. The PSA showed a decrease of costs and effects for both sequential and combination treatment compared to the deterministic model. The median OS was 10.4 months for sequential and 17.6 months for combination treatment compared to the 11.2 and 19.1 months for the deterministic model. The mean cost of sequential treatment was € 766 cheaper and 0.06 QALY less effective compared to the deterministic model. For combination treatment this was € 2,168 cheaper and 0.12 QALY less effective. Resulting in an ICER of € 53,538 which was € 4,366 higher than the ICER calculated in the deterministic model.

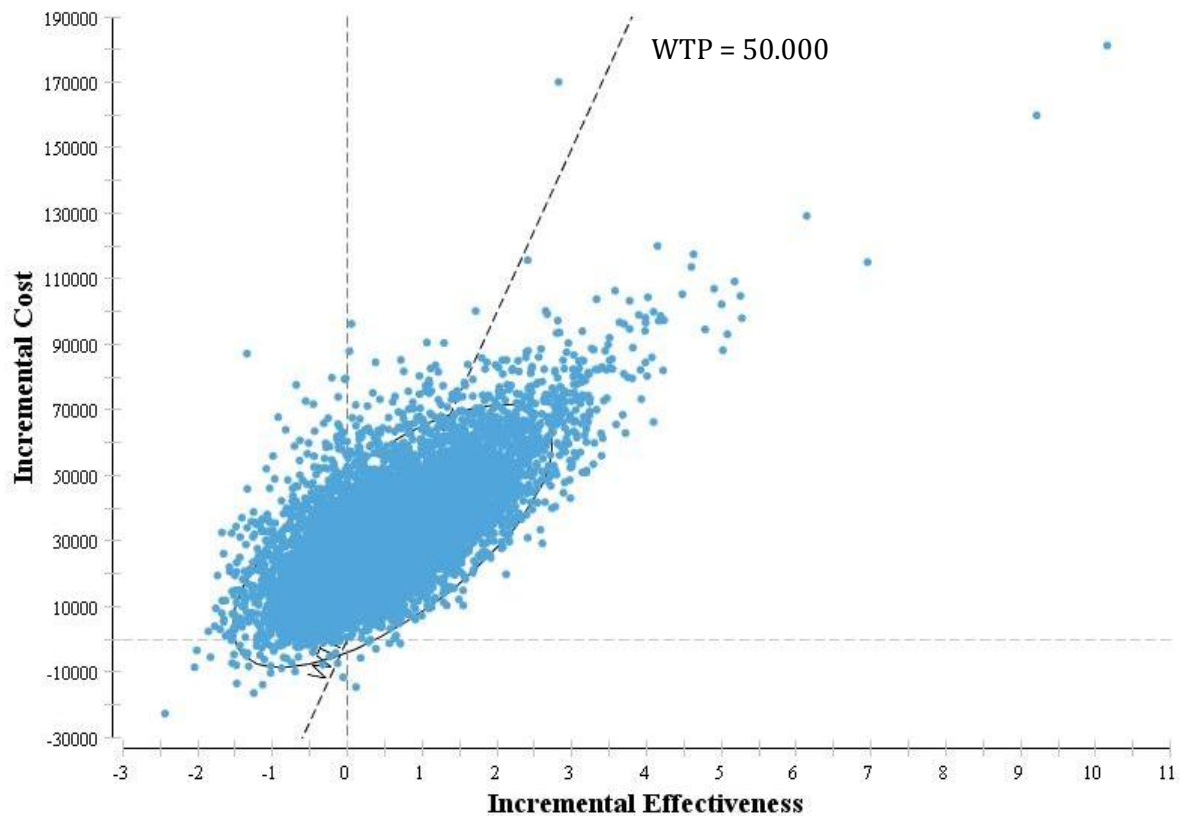
When the parameters were jointly altered in the PSA the sequential treatment was less effective and cheaper than the combination treatment. Higher effectiveness can be reached for higher costs. Where the ICER does not exceed the upper WTP limit of € 50,000 per QALY gained in the deterministic model, it does exceeds this limit in the PSA. This would state a preference of sequential treatment, since holding the WTP threshold means that the benefit of combination treatment over sequential treatment comes at unacceptably high costs.

Table 13. Outcomes of the deterministic versus the probability sensitivity analyses model.

Parameter	Treatment	Costs (euro)	QALY	ICER (per QALY)
Deterministic	sequential	€ 24,336	0.72	€ 49,172
	combination	€ 50,358	1.25	
Mean PSA	sequential	€ 23,570	0.67	€ 53,538
	combination	€ 48,190	1.13	

The CE-plane represent the ICERs of the 10,000 iterations. The confidence ellipse and the WTP line of € 50,000 are shown in Figure 10. Seventy-one percent of the ICERs stayed under the WTP. Most dots are in the upper right quadrant; indicating that a gain in QALYs occurs at a higher cost.

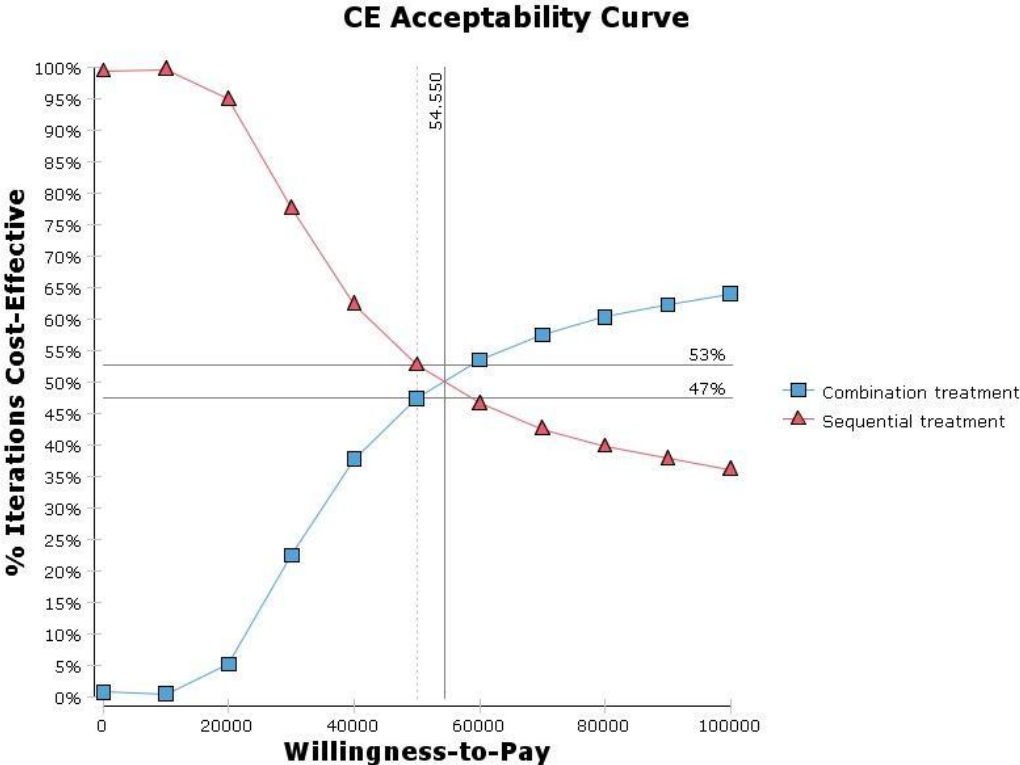
Figure 10. Confidence ellipse of incremental cost-effectiveness of combination versus sequential treatment.



The cost effectiveness of both sequential and combination treatment were used to draw a cost-effectiveness acceptability curve (CEAC) as shown in Figure 11. The CEAC shows the probability that the ICER is below the WTP against the WTP threshold for a number of different thresholds.

At a WTP of € 50,000 the probability that sequential treatment is cost-effective is 53%, for combination treatment this was 47%. In 36% of the sequential iterations the incremental costs per QALY exceed the € 100,000, for combination treatment this was 64%. Under € 54,550 per QALY the probability that sequential treatment is more cost-effective is higher and for combination treatment this is over € 54,550 per QALY.

Figure 11. Cost-effectiveness acceptability curve for sequential and combination treatment.



5.2.3 Discounting

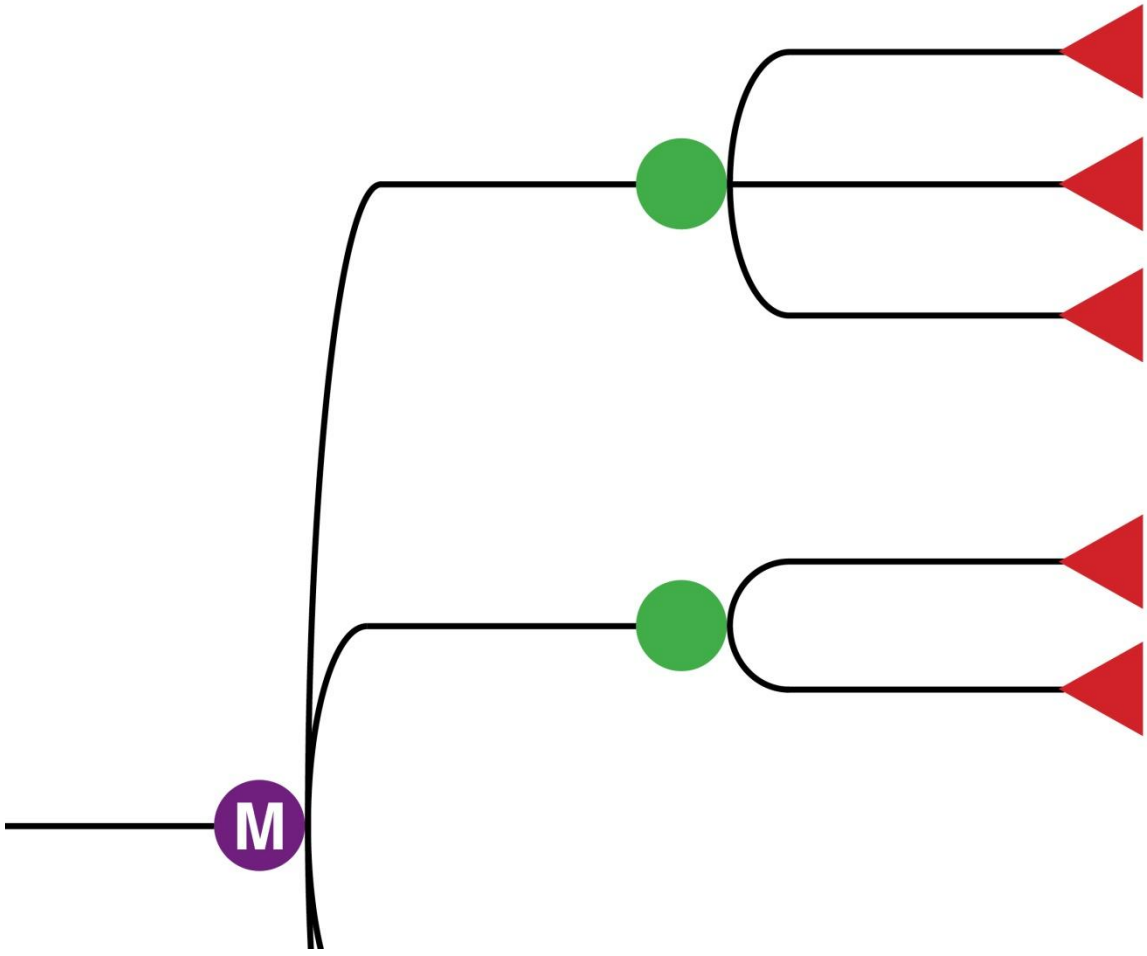
Future costs and benefits are discounted to reflect the time preference that money spend or benefits gained in future should not weight as heavily as money spend or benefits gained today. People prefer to have resources now more than resources in future, because then they can benefit from it in the interim.

Tabel 14. Discounted and undiscounted QALYs, Costs and ICERs.

	Sequential treatment		Combination treatment	
	Discounted	Undiscounted	Discounted	Undiscounted
QALY	0.74	0.72	1.25	1.29
Costs	€ 24,336	€ 25,256	€ 50,358	€ 53,158
ICER			€ 49,172	€ 50,556

The ICER increases from € 39,373 to € 40,601 per LY gained when costs and effects are not discounted. As shown in table 14, the ICER increases to above the WTP of € 50,000 per QALY gained when costs and effects are not discounted.

6 Discussion



6.1 General findings

In this thesis a Markov Model was used to examine the cost-effectiveness ratio of sequential treatment compared to combination treatment for patients with mCRC that are ineligible for curative treatment. This was done from a hospital perspective with real world patient level data available from the pilot outcome research, supplemented by data from the CAIRO trial.

Sensitivity analyses had been used to evaluate the impact of the parameters used in the deterministic model; the models conclusion remained under this sensitivity analyses.

The ICER of combination treatment was € 49,172 per QALY gained compared to sequential treatment, in the PSA the mean ICER per QALY gained was € 53,538. Seventy-one percent of the ICERs did not exceed the WTP limit of € 50.000 per QALY.

The CEAC showed that in 47% of the combination and 53% of the sequential treatment iterations, the ICER per QALY gained was under € 50.000. The tornado-diagram for the OSA showed that chemotherapy costs for first line combination treatment had the highest impact on the ICER, followed by the total other costs of combination treatment. The OSA on transition probabilities showed that the lower Kaplan-Meier changes the ICER to € 5,345 per QALY of sequential over combination treatment, compared to € 40,155 per QALY for combination over sequential treatment for the original and € 68,517 per QALY for combination over sequential treatment for the higher Kaplan-Meier curves.

6.2 Limitations

A number of limiting choices and assumptions were made while developing the model. These assumptions can be divided into assumptions regarding the model structure, the input parameters and the sensitivity analyses.⁴¹ In the following paragraph the limitations of the model are discussed.

6.2.1 Model structure

The model compares sequential and combination treatment. The estimates of these treatments were based on both eligible and ineligible patients. The CAIRO trial excluded patients that did not reach the eligibility criteria. The outcome research made a separate category of the ineligible patients. Eligible and ineligible patients are not comparable, but ineligible patients are a major part of the daily practice population. Despite the disadvantages there is chosen to include the eligible patients. This is done by including the ineligible patients in the sequential and combination treatment groups. In this way the eligible and ineligible patients are not compared with each other, but two groups of eligible and ineligible patients together are compared with each other.

The first model designed for this thesis is shown in appendix F. With the available patient level data it was not possible to calculate the transition probabilities towards and from the relapse states. The relapse state would have included patients that quit the treatment line but had not yet started the next treatment line. The relapse state would have included patients within two treatment lines, patients with severe toxicity or patients with a treatment free interval. The decision has been made to not incorporate these states in the model, but rather to extend the current model states to include this time spent not receiving active treatment. Therefore patients will stay longer in a treatment line than that they were being treated.

The time in a treatment line is used to calculate the weighted averages. Since patients will stay longer in the treatment line than that they were being treated the chemotherapy costs can be overestimated. This will occur in both treatment arms and therefore the effect on the ICER is expected to be reduced.

Wastage is the quantity of a chemotherapeutic drug that is left if the volume of a vial is not equal to the administered dosage. No wastage has been calculated since the chemotherapeutic drugs that were included in this thesis are relatively common and one might expect that any remaining drug would have been administered to another patient. This will not always be the case, especially not in smaller hospitals. The chemotherapy costs can therefore be higher than assumed in this thesis. In the combination treatment arm the underestimation of the costs would be higher, since there more drugs were administered at the same time. The ICER would be expected to be higher when wastage was included in the cost calculation.

The time of a cycle was set as 90 days and the time horizon of the model was set as five years; 20 cycles of almost 3 months. In some observed cases the OS exceeds 20 months, this more than double the generally observed OS for mCRC patients treated with chemotherapy. The cycle length and models' time horizon are common used in mCRC and the same as used in the stage III colorectal part of the outcome research.

Literature suggest a willingness-to-pay threshold around € 50,000 per QALY gained.⁴² The two-year survival rate is approximately 20 to 25% and generally the worst the disease the higher the WTP threshold. Since mCRC is a life-threatening disease the threshold was set on the highest bound; € 50,000 per QALY gained.

6.2.2 Parameters

This thesis is based on data from 2003 and 2004 collected retrospectively. Current the OS of mCRC patients has increased since targeted therapies became available and the supportive care has improved. The data used in this thesis can be stated as outdated, but the chemotherapeutic regimens that were included are still widely used. The question if sequential or combination treatment is more cost-effective is still relevant, since the new therapies are together with these chemotherapies. An additional argument is that it is always good to check if the use of another model on the same data creates different outcomes.

The primary data source was the oxaliplatin pilot outcome research, for the purpose of the Dutch policy regulation of expensive medication. The focus of this outcome research was on oxaliplatin; therefore it can be that there was less focus on the data collection of oxaliplatin-free treatments.

Patient level data was not available on costs and utilities; therefore data was abstracted from the CAIRO trial. Since the patients of this thesis, the outcome research and the CAIRO trial were all from the same source population this was seen as the best alternative.

The QLQ-C30 mapping model used in the outcome research to produce health utilities from the HRQoL was not validated for mCRC. The mapping model has been developed using data on multiple myeloma and was later been validated in non-Hodgkin cancer. The model was used before on haematological cancers in which it provided stable outcomes. Since there was no validated model for mCRC and there were stable outcomes no problems were expected to occur by using the QLQ-C30 mapping model.

Survival bias is a common problem for the collection of QoL data. Patients that are in a very bad health status will not be able to participate on the QoL survey, therefore the study will only represent the healthier patients. Besides this the QoL as experienced by patients can increase when their situation remains the same. Patients get used to their new health status and life expectancy and therefore they experience their QoL better. In the utility table (Table 9) there was also a bias; the utility does not really decrease over time and even increases from 90 weeks on; the same period as where the number of respondents drops below 30 patients.

No patient level data of the used dosage was available. Therefore the calculation of chemotherapy costs were calculated based on the standard dosages recommended for the different treatments.

This thesis is based on cost data from 2009, the patent of oxaliplatin has been expired since. It can be expected that the cost-effectiveness of combination treatment arm would decrease more than the sequential treatment arm, since oxaliplatin was used more often in the combination treatment arm. If the chemotherapy costs are calculated with the current cost data it can be expected that the ICER of combination over sequential treatment will decrease.

As stated before the total other costs are abstracted from the outcome research. Real-life data was only available of a limited group of patients; a maximum of 57 patients for monotherapy and a minimum of 11 patients for the costs of ineligible patients and 11 patients receiving irinotecan combination treatment. Within this limited available data created uncertainty around the costs data.

Weighted averages have been calculated to represent costs per treatment line. This is not an ideal situation. It creates a lot of uncertainty around the costs data.

The hospital perspective is used in this thesis. Normally this would not include patients travel expenses. Patients travel expenses are included in the societal perspective. Most parameters of the societal perspective are not expected to make a difference between both treatment arms. The patients travel expenses was included in the outcome research, since it were the patient's only costs, the treatment itself will be covered by insurance.

6.2.3 Sensitivity analyses

In the PSA of this thesis the beta distribution for both transition probabilities and effects. For the costs a triangular distribution has been chosen. We assumed that a triangular distribution would fit the cost data good enough. There is uncertainty around this decisions because the distributions will not totally reflect the data.

6.3 Comparison with the outcome research and the CAIRO trial

In both the CAIRO trial and the outcome research no ICERs were calculated for stage IV patients. Comparison therefore will focus on OS and costs.

In the CAIRO trial the median OS for sequential treatment was 16.3 months, for the eligible patients in the outcome research this was 11.2 months. For combination treatment the median OS was 17.4 months in the CAIRO trial and 15.1 months for the outcome research. In the outcome research eligible and ineligible patients were not combined. In this thesis eligible and ineligible patients were combined, resulting in a median OS of 11.2 months for sequential and 19.1 months for combination treatment. The median OS for sequential therapy was the highest in the CAIRO trial (16.3 months), followed by the median OS of this thesis and the outcome research (both 11.2 months). For combination treatment the OS of this thesis was the highest (19.1 months), followed by the CAIRO trial (17.4 month) and lowest for the outcome research (15.1 month). The higher OS for combination treatment can be due to the non-random assignment of patients to a treatment. It is more likely that patients with a lower age or better health-state receive combination treatment than older patients with a worse health-state. The difference in OS for combination treatment between this thesis and the outcome research was already expected in paragraph 4.3.1. There were small difference in inclusion of patients in the patient population of the outcome research and this thesis; the outcome research included 314 patients and this thesis included 320 patients. The median OS of the patient population was 13.3 months for the sequential and 19.7 months for the combination treatment arm, compared to 11.2 months for the sequential and 15.1 months for the combination treatment arm in the outcome research.

The total mean costs for the outcome research were € 19,812 for monotherapy, € 28,200 for oxaliplatin combination treatment, € 44,664 for irinotecan combination treatment and € 13,899 for ineligible patients. Noted that the diversity of treatment agents and drugs applied in daily practice results in a wide cost variation between patients and that these costs are calculated. The total costs as in this thesis were € 24,336 for sequential and € 50,358 for combination treatment arm. The costs in this thesis are higher than the costs in the outcome research. The effects of this thesis were also higher than found in the outcome research. Since there was no ICER calculated in the CAIRO trial or outcome research no comparison can be made. Due to the exclusion of the relapse state it is possible that costs and effects were overestimated. Another explanation can be that the model has a higher median OS than the outcome research. Costs are assigned as long as patients are alive; patients with a higher OS receive more treatment and therefore have higher costs. A small difference is also due to the assignment of end-of-life costs; in the outcome research these costs are not included.

The conclusions of the outcome research were in line with the CAIRO trial and the recommendations found in the Dutch guidelines. This guideline implies that it is not important in which sequence of combination the chemotherapeutic drugs are administered but that it is important that patients are exposed to the different drugs. When the ICER is taken into account it can be stated that, until a WTP of € 50,000, sequential treatment has the highest probability of being cost-effective. Therefore sequential treatment could be recommended to mCRC patients that are ineligible for curative surgery.

6.4 Future research

For future research it would be beneficial to include the relapse state in the model. This would better reflect the costs and yield more detailed information. Therefore more detailed information, about the costs and duration of the treatment period, treatment free intervals and adjuvant or palliative treatment should be recorded.

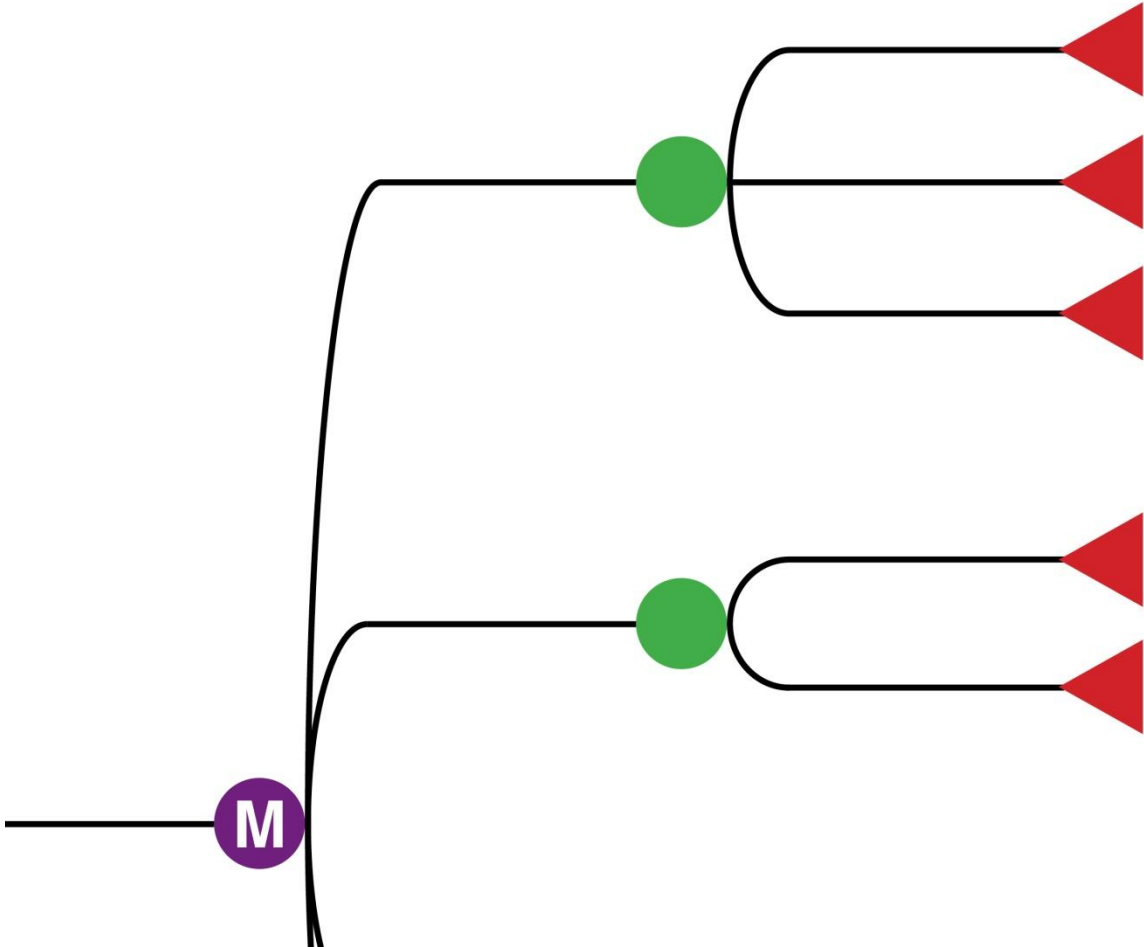
For future research it is necessary to collect patient level data of ineligible patients. Most patients treated in daily practice will not fulfil the eligibility criteria. The data that is represented before as real-world costs-effectiveness data did not represent this big part of the patients.

It would be preferable to collect cost data on patient level, since not it was only available of a limited amount of patients. This data was generalized to the entire patient population and therefore weighted averages were calculated in this thesis. It would also be preferable to collect QoL data on patient level. Utilities are now abstracted from the QoL data from the CAIRO trial. No utility information of ineligible patients was available, therefore ineligible patients were treated as eligible patients in this thesis.

Data was obtained from 2003 and 2004 and for future research collecting up-to-date data would be recommended. Since 2003 costs have changed since patent on oxaliplatin ended and chemotherapeutic drugs are now combined with molecular targeted therapies. This change in treatment increased the OS and therefore the transition probably might change. The extended patent decreases the costs and the gain in OS increase the effects. Using data from 2012 could decrease the ICER dramatically and put it under the upper WTP level of € 50,000.

Since the discussion about the Dutch policy regulation of expensive medication and affordability of healthcare is topic with growing interest, it would be interesting to draw some attention to future research topics. Sequential treatment is more cost-effective till a WTP of approximately € 54,000 so it would be efficient to know what would be the impact on prescribers behaviour if guidance and treatment protocols prefer sequential treatment. What is the patients influence on the chosen treatment? Patients differ in preparedness to get treated and acceptance of adverse events. Better information and assessment of patients could change their opinion about chosen treatment. And do patients still follow the recommendations of the prescriber? All this decisions about the chosen treatment can have major effects on the costs and effects in daily practice.

7 Conclusion



The aim of this thesis was to investigate the real-world incremental cost-effectiveness ratio of combination chemotherapy over sequential chemotherapy in the treatment of metastatic colorectal cancer patients that are ineligible for curative treatment.

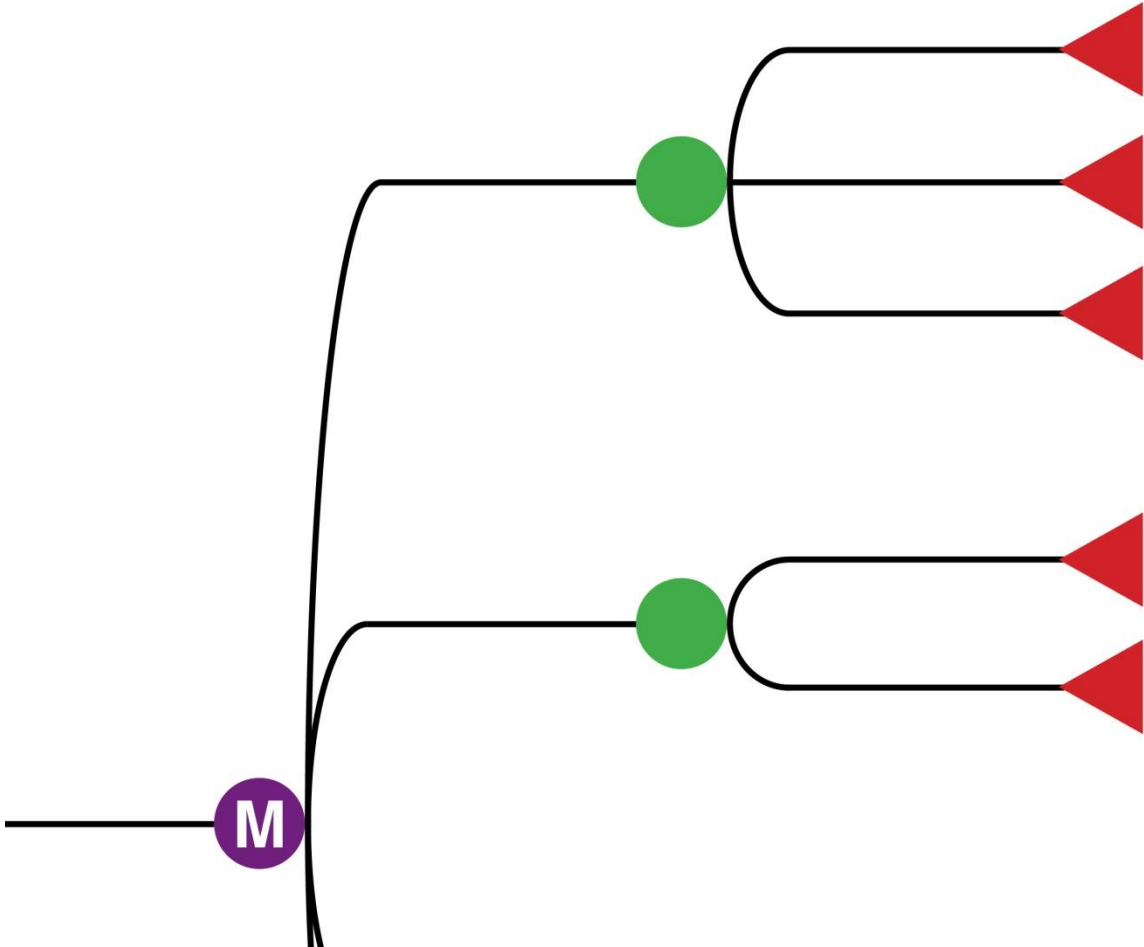
There is no curative treatment for patients with mCRC, with combinations of chemotherapeutic regimens the median overall survival is approximately 20 months.¹⁵ The effectiveness of combination treatment is higher than the effectiveness of sequential treatment, but it comes with higher costs. The OS for in the sequential treatment arm was 11.2 months and 0.72 QALYs, for combination treatment was 19.1 months and 1.25 QALYs. The costs increase when changed from sequential to combination treatment. The costs for sequential treatment are € 24,336 and the costs for combination treatment are € 50,358.

The ICER of combination compared to sequential treatment was € 49,172 per QALY gained, 71% of the 10,000 iterations did not reach the maximum willingness-to-pay of € 50,000 per QALY gained.

The real-world incremental cost-effectiveness ratio of combination chemotherapy over sequential chemotherapy does not exceeds the WTP. Therefore combination treatment is preferred over sequential treatment.

The conclusion of the CAIRO trial was; It is more important that patients are exposed to all three types of chemotherapeutic drugs, than that patients are treated within either the sequential or the combination treatment arm. This thesis shows that combination treatment have a higher median overall survival than sequential treatment. Therefore the change that patients are exposed to all three chemotherapeutic drugs is higher when patients start on combination treatment. This higher OS comes for an acceptable increase in costs.

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