Quality aspects of Dutch colorectal cancer trials

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Chapter 1
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General introduction

Colorectal cancer

Colorectal cancer is one of the most common causes of cancer in the western world. Approximately 50% of patients develop metastases with only a minority being eligible for a metastasectomy with curative intent. The majority can only be considered for palliative systemic treatment. Over the past decades, the options for systemic treatment have improved considerably, from 5-FU as the only available drug to treatment with other cytotoxic drugs such as oxaliplatin and irinotecan, and targeted agents such as antibodies to the vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). These new therapies as well as the more frequent use of surgical resections of metastases have improved median overall survival from approximately 10-11 months to currently about 30 months(1-3).

DCCG

The Dutch Colorectal Cancer Group (DCCG) is a national multidisciplinary clinical research group in The Netherlands that aims to stimulate clinical research and to improve the quality of diagnosis and treatment of patients with colorectal cancer, with practice changing trials. In January 2003 the DCCG initiated the CAIRO study, a randomized phase 3 study in patients with metastatic colorectal cancer (mCRC). Since then 2133 patients with mCRC were treated in three consecutive phase III trials(4-6), and the 4th and 5th study are currently open for accrual(7, 8). CAIRO is a acronym for the drugs used in the first study: CApecitabine, IRinotecan and Oxaliplatin. After the success of this study it was decided to maintain this acronym for subsequent studies. The results of the first 3 trials have been incorporated in national and international guidelines.

The final stage of the development of new drugs or treatment strategies is the conduct of phase III trials in which an investigational therapy or strategy is compared with the standard of care. The primary endpoint of these studies may vary and depends on the context in which the new therapy is used. The final purpose is to improve the outcome of patients either by a benefit in survival or improved quality of life due to less toxicity of equally effective therapies, as quality of life is being increasingly recognized as an important outcome parameter. Obviously, it is essential that this research should be of high quality and meets (inter)national standards of conduct.

The design and conduct of phase III clinical trials requires great effort and resources, since patients trust their (quality) of life to the investigations, while the required number of patients as well as the number of participating centres

is large. These efforts are therefore only justified if the results are expected to be, reliable and clinically relevant. We are also obliged to the participating patients only to include patients in good studies, as they are willing to take the risk of a new treatment which has not be proved to be effective and could have unknown side effects. Therefore the design, conduct, analysis and reporting of clinical trials should be of the highest quality. Although there is not a clear definition or international guideline of what we consider high quality research, several issues can be addressed on this topic. This will be discussed in the next paragraphs.

Protocol design

A clinical trial starts with the design of a protocol. In the Netherlands, a standard protocol has been developed and made available by the Central committee on Research Involving Human subjects (CCMO) which contains all relevant topics that should be addressed. Among others these concern an introduction in which the rationale for the study and the objective(s) are explained; definition of the research population with data on the planned number of patients and feasibility; a statistical paragraph with justification of the design and eligibility criteria for reasons of patients' safety and limitation of selection bias.

In the methods section all study procedures must be described clearly and specifically, i.e. treatment, dose reductions, evaluations, diagnostic tests, and follow-up. This is to minimise procedure variation between individual investigators.

- All clinical trials have to be reviewed by an accredited medical ethical committee(MEC) which has to address the following issues (section 3 WMO):
- The scientific research contributes to new insights in the field of medicine.
- There are no simpler or less intrusive alternatives (for example; preferably no minors or incapacitated subjects).
- The importance of the research is in proportion to the objections (burden) and the risks to the research subjects.
- The study meets the scientific requirements for research.
- The research is led or carried out by professionals.
- Any financial compensation for the research subject does not form part of the reason for participating in the research.
- The protocol states the extent of the benefits for the subjects as a result of participation in the study (in the case of group therapy: the benefits for the group to which the subject is assigned).

One of the issues concerns the risks the research subject is exposed to. During the study this is monitored by the reporting of Serious Adverse Events (SAEs). A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH-GCP article 1.50). Besides the study team SAEs are also monitored by the MEC and the independent data monitoring committee (IDMC).

Accrual
After a protocol has been approved by the ethics committee, the study accrual can start. It is important to realize that in The Netherlands only 3.5 % of the total number of new cancer patients are enrolled in CKTO and EORTC trials, which are the majority of investigator-initiated trials. One of the goals of the Dutch Cancer Foundation is to increase the number of participants in clinical trials (KWF beleidsvisie 2006-2011).
Obviously, a fast accrual facilitates that trial results become available more rapidly, which is in the interest of patients and general healthcare. A slow accrual may endanger the relevance of the primary objective of the trial, the quality of the trial since practice may change over time and more over, trials that are discontinued early due to poor accrual are a waste of resources.

Quality assurance
When the protocol meets sufficient standards in terms of quality and feasibility, the next step is to ascertain the strict adherence to the protocol. Deviations from the protocol may impact on the outcome of the trial obscuring the true effects of the treatment arms. Adherence to the protocol in trials with anticancer drugs consists of specific aspects, such as, the correct preparation of the drugs, administration and dose adjustments in case of toxicity, and the assessment of outcome according to scheduled and prescribed methods.

Research on the quality of cancer clinical trials has been started by the EORTC quality control programmes in radiotherapy studies in the 1980s followed by 3 studies which assessed the quality of chemotherapy(9-12). On-site visits were performed to investigate the structure and process parameters of the quality of chemotherapy, protocol adherence and data quality control. Between institutions large differences were observed in available information in the hospital files, for instance on chemotherapy dosing, date of administration and toxicity registration.

The results of the EORTC studies on quality control have resulted in the introduction of the systemic therapy checklist. This checklist contained

variables related to eligibility, drug doses and administration, biochemical and haematological parameters, variables related to toxicity of treatment and response parameters. The use of this checklist improved the problem of missing data, from 68% correct data before the introduction to 86 % in the hospitals that did not use it, and 98% in the hospitals which did use it. This difference was explained by the decrease in missing data from 28% to 11% in the hospitals which did not use to 0.6% in the hospitals which did use the checklist(10).
Research on the quality of systemic treatment in daily practice mainly focuses on deviations from clinical guidelines. Registration of actual administered chemotherapy and the resulting toxicity were suboptimal according to some assessments(13, 14). Suboptimal dosing and timing of systemic therapy is often due to avoidable reasons. Reasons for variation should therefore be investigated more thoroughly. Some advocate that better protocols in daily practice would lead to improvement in quality of care in daily practice (15). Because treatment in a clinical trial is well described in the protocol it might therefore result in better quality of care for cancer patients compared to treatment in daily practice. Many studies have tried to compare outcome between trial-participants and non-trial participants, but few data are available concerning a difference in quality of care.

Publication
For the publication of clinical trials the Consolidated Standards of Reporting Trials (CONSORT) group has developed a checklist and a flow diagram to improve reporting of RCTs. A study on the quality of reporting trials in scientific journals, showed that many items remained underreported in oncological studies(16).

Outline of this thesis

As there are no clear guidelines for assessing the quality of clinical trials that include the previously mentioned items, we investigated quality of a number of aspects in the CAIRO studies.
During the first CAIRO study we observed many SAEs that clearly required further follow-up. This resulted in an on-site monitoring of all fatal SAEs. The results of this quality control are described in **chapter 2.**
With more than 2000 included patients in the currently completed CAIRO studies, with 60%-to 80% of Dutch hospitals participating, this allowed us to study the quality of colorectal cancer clinical trials in The Netherlands. Because treatment in the first CAIRO trial was similar to treatment in daily practice we were able to compare the outcome of patients treated in this trial with those treated outside the trial in daily practice. This is described in **chapter 3.**
We observed large differences in WHO Performance Score (PS) reporting and QoL scores. As an example, a physician scored the WHO PS of a patient as 0, while the patient reported to be unable to walk even a short distance. In **chapter 4** we compare the prognostic value of patient reported QoL and physician reported WHO PS.
Finally, it is often stated that protocol adherence is lower in centres with poor accrual (i.e. less than 5 patients) compared to centres with high accrual, and that low accruing centres may therefore harm the quality of the trial. In The Netherlands hospitals can be divided according to size and infrastructure in regional hospitals, STZ hospitals and academic hospitals. We investigated whether there is a difference in quality of trial performance between these type of hospitals. In **chapter 5** we address this issue and try to find factors which can explain differences between hospitals.

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Chapter 2

A prospective monitoring of fatal serious adverse events (SAE) in a Dutch Colorectal Cancer Group (DCCG) phase III trial (CAIRO) in patients with advanced colorectal cancer.

Annals of Oncology. 2010;21(2):415-8.

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Abstract

Background
Early and correct assessment of treatment-related mortality is highly important in clinical cancer trials. However, no data are available on the quality of safety monitoring.

Patients and methods:
An on-site review was performed by the study coordinators of the individual charts of all patients participating in the CAIRO study (1) who had died within 30 days of the last administration of study drugs when death was accompanied by any other event than disease progression. The relationship between treatment and death was categorized as unrelated, remote, possible, or probable, and submitted to an independent data monitoring committee (IDMC). These results were then compared with the initial assessment of the local investigator.

Results:
Forty out of 820 patients qualified for review. The relationship between cause of death and study drugs was changed in 26 patients (65%). A major protocol violation (MPV) was identified in 12 out of 14 patients with a probable relationship between cause of death and study treatment.

Conclusions:
There was little agreement between the relation as assessed by the local investigator compared to the IDMC. A quality control improves the assessment of safety results and the observed MPVs underscore the importance of educating medical staff and patients.

Introduction

An important aspect of clinical trials in cancer patients is an early and reliable assessment of the relationship between adverse events and treatment. For a timely update of this crucial information, serious adverse events (SAE) have to be reported according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. As defined by ICH-GCP, a SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH-GCP article 1.50). Most study protocols define a period during which SAE have to be reported, and usually this is from the signing of the informed consent form until 30 days after the last administration of study drug(s). This implies that in clinical trials all hospitalizations and deaths occurring within 30 days of last study drug administration have to be reported within 24 hours. The SAE reports are centrally collected, assessed by the principal investigator(s) (PI) and/or study coordinators, and finally submitted to an independent data monitoring committee (IDMC).
The IDMC consists of independent experts to assess intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH-GCP article 1.25). Within this system the early safety monitoring of clinical trials by the PI and IDMC largely depends on the early and reliable assessment of SAE reports.
Although SAE reports are the most important way to monitor the early safety and to assess the treatment-related mortality, there is no information available about the quality of SAE reporting by the local investigators. We performed a quality control on the reporting of SAEs in a large prospective randomised phase III trial.

Patients and methods

In the CAIRO study of the Dutch Colorectal Cancer Group (DCCG) (1;2) registered with ClinicalTrials.gov with the number NCT00312000, 820 patients with advanced colorectal cancer (ACC) from 74 Dutch hospitals were randomized between 1st line capecitabine, 2nd line irinotecan, and 3rd line capecitabine + oxaliplatin (sequential treatment arm) versus 1st line capecitabine + irinotecan, and 2nd line capecitabine + oxaliplatin (combination treatment arm). Registration of patients was performed by a telephone call or fax of the local investigator with the central datamanagement office, which included a confirmation of all eligibility criteria. A protocol summary and checklist which summarized the eligibility criteria, treatment and evaluation

schedule and recommended dose modifications for the most frequently expected toxicities was made available to all investigators for inclusion in to the file of each participating patient. Furthermore, prior to the initiation of the study three regional investigators meetings were organised to inform investigators and other research staff about the protocol. The protocol contained specific instructions for eligibility both for study entry as well as for the initiation of subsequent treatments. As a prospective part of the protocol, patients who had died within 30 days of the last administration of study drugs and whose death was accompanied by any other event than disease progression, irrespective of the causality reported for this event by the local investigator, were selected for this analysis. The study coordinators (MK, CJAP) performed an on-site review of the individual charts of these selected patients, and they assessed the relationship between treatment and death based on all available documentation. The relationship of the event to study treatment was categorized as either unrelated, remote, possible or probable, as was also previously done by the local investigator on the SAE form. The results of the assessment by the study coordinators as well as the original SAE reports were submitted to the IDMC, who made the final assessment of causality.

Results

Study population

Of the 820 patients enrolled in the study a total of 746 SAE's were reported in 443 patients. These SAE reports included 630 hospitalizations, 112 deaths occurring within 30 days of last administration of study drugs and 4 other reasons. Of these 112 deaths, 9 were reported ≤ 24 hours, 42 ≤ 2 weeks, and 70 > 2 weeks after the date of the event, with a median time of reporting of 34 days (range 0 – 1261). In 72 out of these 112 cases, disease progression was the obvious single reported cause of death. The remaining 40 patients were eligible for on-site review. The characteristics of these 40 patients did not differ from the overall study patient population except for age (median 68 years (range 52-79) vs 63 (27-84) years respectively, $p<0.01$).

Review results

Of the 40 patients whose charts were reviewed, the local investigators assessed the relationship between their death and the study medication as unrelated in 14, remote in 6, possible in 9 and probable in 11 patients. The study coordinators assessed the deaths as unrelated in 2, remote in 10, possible in 14 and probable in 14 (Table 1). The assessment by the study coordinators was confirmed by the IDMC in all cases. Compared to the assessment of the local investigators as documented on the original SAE reports, the relationship between cause of death and study drugs was changed by the review in 26 patients (65%). In 20 patients (50%) the study coordinators increased the level

of causality, with in three patients the causality even being changed from unrelated to probable.

		IDMC				
		Unrelated	Remote	Possible	Probable	Total
Local investigator	Unrelated	2	4	5	3	14
	Remote	0	2	4	0	6
	Possible	0	2	3	4	9
	Probable	0	2	2	7	11
	Total	2	10	14	14	40

Table 1 Causality assessed by local versus the IDMC

Protocol violations

In the 14 patients whose death was established after review as probably related to study treatment, the causes of death were neutropenic sepsis (n=8), neutropenic fever (n=2) and dehydration due to diarrhoea (n=4) (Table 2). In 12 of these 14 patients one or more major protocol violations (MPV) were identified. These concerned the administration of chemotherapy despite an abnormal renal function (n=1), the administration of irinotecan despite elevated serum bilirubin concentration (n=2), continuation of capecitabine therapy despite previous or ongoing severe diarrhoea (n=7), and continuation of study drugs despite a decreased WHO performance status of ≥ 3 (n=4). In five of these 12 patients the MPVs had already been identified by the regular data management, and in seven they were identified during the review. In addition to these MPVs, four patients were considered ineligible for study participation which was not detected after standard data processing. The reasons for ineligibility were prior systemic treatment for advanced colorectal cancer (n=2), WHO PS 3 and partial bowel obstruction (n=1), and abnormal renal function at baseline plus severe leucopenia during prior adjuvant chemotherapy (n=1).

Nr	Arm	Line	Cycle	Cause of death	Protocol violation
1	A	1	1	Neutropenic fever	Not eligible: abnormal renal function plus severe leucopenia during prior adjuvant chemotherapy
2	A	1	2	Neutropenic sepsis, dehydration due to diarrhoea and vomiting	Continuation of capecitabine despite of diarrhoea grade 2
3	A	1	3	Diarrhoea	Not eligible: prior chemotherapy for advanced disease Continuation of capecitabine despite of diarrhoea
4	A	1	4	Diarrhoea	Continuation of capecitabine despite of PS WHO grade ≥3 and diarrhoea grade 3
5	A	1	4	Neutropenic sepsis	No dose reduction despite of PS WHO grade ≥3 and grade 3 nausea, vomiting and diarrhoea
6	A	1	4	Sepsis and diarrhoea	Continuation despite of recurrent grade 3 diarrhoea
7	A	2	1	Neutropenic sepsis	Elevated serum bilirubin at start of irinotecan
8	A	2	1	Neutropenic sepsis	Elevated serum bilirubin at start of irinotecan
9	A	2	2	Neutropenic fever	None
10	A	2	31	Neutropenic sepsis, diarrhoea	No dose reduction of capecitabine despite of recurrent grade 3 diarrhoea
11	B	1	1	Neutropenic sepsis	None
12	B	1	1	Neutropenic sepsis	Not eligible: WHO PS 3 and partial bowel obstruction Chemotherapy given despite of WHO PS grade ≥3
13	B	1	1	Neutropenia, diarrhoea	Continuation of capecitabine despite of diarrhoea grade 3
14	B	1	2	Neutropenic sepsis, dehydration due to diarrhoea and vomiting	Continuation of capecitabine/irinotecan despite of PS WHO grade ≥3 and diarrhoea grade 2

Table 2 Treatment-related deaths A= sequential chemotherapy, B=Combination chemotherapy, PS = performance status

Discussion

To our knowledge this is the first randomised phase III trial in which the quality of the SAE reporting was prospectively assessed. For our review 72 of the 112 SAEs reporting a death occurring within 30 days of the last administration of study drugs were excluded because the cause of death was disease progression and no other concomitant medical events were reported. Although we did make an effort to obtain additional information to confirm this, we acknowledge that this may have introduced a selection bias by which we underestimated the number of treatment-related deaths. However, the objective of our review was not a meticulous quantitative analysis, but a study to assess the quality of SAE reporting.

We recorded a disagreement between the assessment of the local investigators and the IDMC on the relationship between the study drugs and death in 65% of the patients whose charts were reviewed. Local investigators frequently underestimated the relation between the administration of study drugs and death. The CAIRO study tested the optimal use of well established cytotoxics (capecitabine, irinotecan, and oxaliplatin), and all participating investigators had previous experience with the use of these drugs. However, insufficient knowledge about the safety profiles and management of toxicities cannot be excluded as a cause for the observed underestimation. Another possibility is that the short reporting period of 24 hours after the occurrence of the SAE may not always allow a full and comprehensive assessment of the SAE. We assume this underestimation is not limited to SAEs reporting death, but applicable to the reporting of SAEs in general. However, this was not investigated.

Of concern is the fact that a MPV was involved in 12 out of the 14 treatment-related deaths. The most frequently occurring MPV was the continuation of capecitabine despite the presence of diarrhoea. The cause of death of two ineligible patients in this review was probably related to study treatment (patient 1 and 12 in table 2). In both patients, the reason of ineligibility likely played a role in the observed toxicity leading to death. Another two patients were ineligible for second-line treatment with irinotecan because of an elevated serum bilirubin, and these patients subsequently died of febrile neutropenia. This underscores the importance of educating investigators and patients in order to prevent unnecessary severe toxicity and of checking all relevant data prior to randomization and initiation of treatment cycles. As described in the methods, a protocol checklist containing the most relevant information on this subject were distributed to all investigators, but we have no information as to its use. Meetings were also organized to inform the investigators about the protocol. This is more than the average trial, therefore we believe the results do not reflect shortcomings in the study organization but a general problem in clinical trials.

The results of similar reviews have been published, however these were only performed in retrospect upon the occurrence of unexpected severe toxicities. Examples in metastatic colorectal cancer studies are EORTC study 40015(3) and Intergroup study N9741(4) . EORTC study 40015 (3) was closed after 8 deaths unrelated to disease progression had occurred. The individual hospital files were inspected and discussed with the physician to determine whether the observed deaths were related to or exacerbated by the study treatment. Four deaths were considered as related, three as exacerbated, and one as unrelated to study treatment. In the Intergroup study N9741(4), a panel of 5 independent medical oncologists reviewed the causes of the observed early deaths. Of the 23 observed deaths, 16 were assessed as treatment-related after central independent review. Both reports did not present information on any initial discrepancy between the assessments of local investigators and study coordinators or independent panel, or on the involvement of any MPV that could have attributed to treatment-related deaths. In this respect our results are unique, at least to our knowledge. We believe that such information provides relevant data, which contribute to an accurate interpretation of study results.

In conclusion, a quality control by on-site review of hospital charts of patients experiencing SAEs may improve the quality of the assessment of treatment-related mortality. This process revealed relevant and new information, such as MPVs and patient ineligibilities. This implies that the assessment by the local investigator may not reflect the true relationship between a SAE and the study medication, and that routine datamanagement may not reveal all relevant information. Our data should make investigators and datamanagers aware of these pitfalls. The implementation of novel information and communication technologies may add to prevent protocol violations as described.
The implementation of planned reviews as described here as a routine part of clinical studies should lead to a better quality of reported data. The review of treatment-related mortality is being continued in subsequent CAIRO studies (5), and a quality control program has been initiated in which other aspects such as protocol adherence are investigated.

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Chapter 2b

Bevacizumab and cancer treatment-related mortality

JAMA. 2011;305(22):2291-2293.

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Linda Mol
Miriam Koopman

2b

Bevacizumab and cancer treatment-related mortality

To the Editor: Dr Ranpura and colleagues performed a meta-analysis on treatment-related mortality with bevacizumab in cancer patients.[1] The authors referred to results of our research that showed a higher overall risk of FAEs in cancer patients due to serious toxic effects of chemotherapy.[2] We monitored FAEs in a study of 820 patients with metastatic colorectal cancer.[3] One of our main findings, after reviewing individual records of patients experiencing FAEs, was a difference in the assessment of the relationship between FAEs and treatment between treating physicians and an independent data monitoring committee in 65% of patients. Furthermore, we found that major protocol violations were involved in the majority of FAEs, which implies that these FAEs could have been prevented by more adequate patient care. Therefore, we ask the authors whether such monitoring was performed on the FAEs in the studies included in their meta-analysis. This would allow a better assessment of the possible relationship of FAEs with bevacizumab treatment and would provide insights into whether certain FAEs could have been prevented by better adherence to treatment guidelines.

We also question the inclusion in the meta-analysis of studies performed in patients with pancreatic and prostate cancer, for which bevacizumab is not approved. Of all 6 tumour types that the authors included in their analysis, the relative risk of FAEs in these 2 tumour types ranked first and third, respectively, and therefore the results in pancreatic and prostate cancer had a relatively large effect on the overall result. A tumour-specific interaction between bevacizumab and tumour type in terms of toxicity cannot be excluded, as is suggested in the case of non–small cell lung cancer with squamous cell histology, and bevacizumab-related toxicity may thus have contributed to the negative outcome of studies in pancreatic and prostate cancer. Therefore, we would consider it more relevant for daily practice if only data from approved indications would have been used.

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Chapter 3

Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands.

Acta Oncologica. 2013 Jun;52(5):950-5.

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3

Abstract

Introduction
The external validity of trial results is a matter of debate, and no strong evidence is available to support whether a trial may have a positive or a negative effect on the outcome of patients.

Methods
We compared the results of stage IV colorectal cancer patients treated within a large Dutch phase III trial (CAIRO), in which standard chemotherapy and standard safety eligibility criteria were used, to patients treated outside the trial during the trial accrual period in a representative selection of 29 Dutch hospitals. Non-trial patients were identified by the Netherlands Cancer Registry (NCR), and were checked for the trial eligibility criteria.

Results
The NCR registered 1946 stage IV colorectal cancer patients who received chemotherapy, of whom 394 patients were included in the CAIRO trial and 30 patients in other trials. Thus, the CAIRO trial participation rate was 20%. In the 29 hospitals, 162 patients received chemotherapy in the trial and 396 patients received chemotherapy outside the trial. Of the non-trial patients, 224 patients fulfilled the trial eligibility criteria. The overall survival of eligible non-trial patients was comparable to trial patients (HR 1.03, $p=0.70$). However, non-eligible non-trial patients had a significantly worse outcome (HR 1.70, $p<0.01$).

Conclusion
These data provide evidence in a common tumour type that trial results have external validity, provided that standard eligibility criteria are being observed. Our finding of a worse outcome for patients not fulfilling these criteria strongly argues against the use of cancer treatments in other patient categories than included in the original trials in which these treatments were investigated.

Introduction

Clinical trials are an essential tool for the evaluation of novel medical drugs and technologies, and the results of these trials provide the strongest backbone of evidence-based medicine. Clinicians often assume that trial participation is beneficial for the individual patient, mainly because of the increased attention given to trial patients as compared to patients treated in daily practice. However, earlier reviews [1-4] have not provided strong evidence that trial participation improves outcome, although a trend towards a positive effect was noted. These reviews identified differences in interventions as well as patient characteristics in- and outside trials as possible confounders. In a more recent systematic review, which was not restricted to cancer trials, no evidence was found for either a beneficial or a harmful effect of trial participation [5].
We have conducted a national multicentre investigator-initiated prospective randomized phase III trial in metastatic colorectal cancer patients on the sequential versus the combined use of standard cytotoxic drugs: capecitabine, oxaliplatin and irinotecan [6,7]. The study medication of this trial concerned standard drugs and regimens, which therefore provided the opportunity to compare the outcome of trial patients with patients who were treated with chemotherapy outside the trial during the trial accrual period. This analysis also allowed to assess the trial participation rate. We here present the results of this analysis.

Materials and Methods

Patients participating in the trial
Between January 2003 and December 2004, 820 metastatic colorectal cancer patients were included in the investigator-initiated phase III randomized CAIRO trial (ClinicalTrials.gov NCT00312000) of the Dutch Colorectal Cancer Group (DCCG)[6,7]. Of these, 396 patients presented with stage IV disease (i.e. synchronous metastases), of whom 2 patients were later found ineligible and were therefore excluded from the survival analysis. CAIRO is the only trial to date in which the sequential versus the combined use of all 3 cytotoxic drugs with efficacy in colorectal cancer has been prospectively investigated. Patients were randomized between first-line capecitabine, second-line irinotecan, and third-line capecitabine + oxaliplatin (sequential treatment arm) and first line capecitabine + irinotecan and second-line capecitabine + oxaliplatin (combination treatment arm). All cytotoxic drugs were administered at their recommended doses and schedules, and treatment was required to start within one week of randomisation. The main eligibility criteria included histologically proven colorectal cancer in an advanced stage not amenable to curative surgery, measurable or assessable disease parameters, and no previous systemic

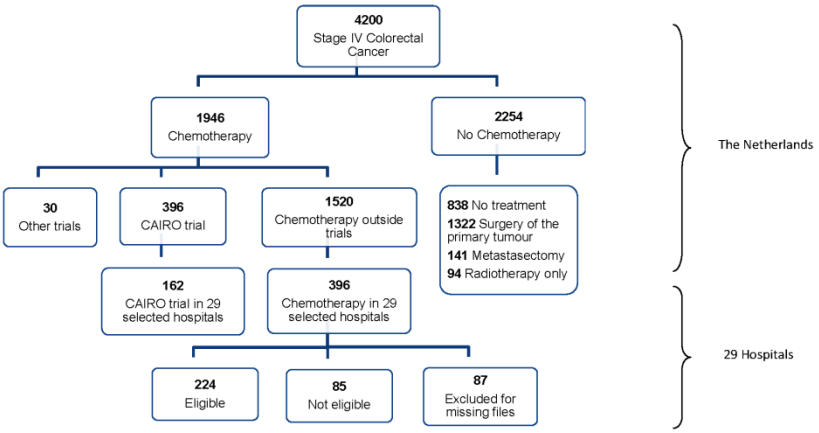
treatment for advanced disease. Previous adjuvant chemotherapy was allowed provided that the last administration was given at least 6 months before randomisation. Eligible patients were required to have a WHO performance score of 0-2 and adequate hepatic, bone marrow and renal functions. Exclusion criteria included serious concomitant disease preventing the safe administration of chemotherapy or likely to interfere with the study assessments; other malignancies in the past 5 years with the exception of adequately treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin; pregnancy or lactation; patients with reproductive potential not implementing adequate contraceptive measures; central nervous system metastases; serious active infections; inflammatory bowel disease or other diseases associated with chronic diarrhoea; previous extensive irradiation of the pelvis or abdomen; concomitant administration of any other experimental drug; concurrent treatment with any other anti-cancer therapy. A total of 79 of the approximately 100 Dutch hospitals participated in this study.

Patients not participating in the trial

Non-trial patients were identified by using data from the Netherlands Cancer Registry (NCR), which registers all cancer patients at primary diagnosis. This implies that metastatic patients are only registered when they present with synchronous metastases, i.e. stage IV. Therefore, non-trial patients with metachronous metastases could not be included in the analysis. All stage IV colorectal cancer patients who were diagnosed during the CAIRO trial accrual period and who received chemotherapy were identified in the NCR.

Comparison of trial with non-trial patients

For reasons mentioned above, the comparison was restricted to stage IV patients. To compare the outcome between trial and non-trial patients, non-trial patients were identified. For a more detailed analysis, 29 hospitals were selected which were considered to be representative for Dutch healthcare (3 university hospitals, 14 large teaching hospitals, and 12 general hospitals). This was further checked by comparing the median overall survival of all stage IV patients in these 29 hospitals with all other patients identified by the NCR. Of these 29 hospitals, 26 hospitals participated in the CAIRO trial. The medical files of all stage IV colorectal cancer patients who received chemotherapy outside the CAIRO trial in these 29 hospitals were reviewed. Data were collected on baseline characteristics, CAIRO eligibility criteria, treatment schedule, and survival. These data were compared with data from stage IV patients included in the CAIRO trial. Trial participation was assessed by comparing the number of patients included in the CAIRO trial with the **Figure 1:** Flow chart of the 4200 patients who were diagnosed w ith stage IV colorectal cancer during the CAIRO trial accrual period.



total number of patients who did not participate but would have been eligible for the CAIRO trial.

Statistics

Baseline patient characteristics of trial versus non-trial patients were compared using the Students t-test for continuous variables and χ^2 test for dichotomous or nominal values. Overall survival was calculated in all patients from the date of diagnosis until death or censored on the date last known to be alive. This was done to allow a fair comparison of trial versus non-trial patients. Of note, the overall survival in the CAIRO trial was originally calculated from the date of randomisation.

The median overall survival was estimated using the Kaplan-Meier method, and trial patients were compared to non-trial patients by means of the logrank test. Multivariable analysis was performed with the Cox-Proportional Hazards Model. The analyses were performed with SPSS statistical software (version 18). All statistical tests were 2-tailed, using a 5% significance level.

Results

During the accrual period of the CAIRO trial, 4200 patients were registered by the NCR with stage IV colorectal adenocarcinoma, of whom 1946 patients received palliative chemotherapy (Fig. 1). Of these, 396 patients were included in the CAIRO trial, 30 patients in other ongoing trials, and 1520 patients received chemotherapy outside the scope of trials. Of the 2254 patients who did not receive chemotherapy, 838 patients did not receive any treatment,

1322 patients had a resection of the primary tumour of whom 141 patients also had a metastasectomy, and 94 patients were treated with radiotherapy.
In the 29 selected hospitals, the NCR identified 558 stage IV CRC patients who received chemotherapy, of whom 162 patients were included in the CAIRO trial and 396 patients received chemotherapy outside the trial. The median overall survival in these 396 patients from these 29 hospitals did not significantly differ from the total of 1120 patients with stage IV disease who have received chemotherapy as identified by the NCR (data not shown), supporting the representability of the 29 hospitals. After review of the medical files of these 396 patients, 224 patients were identified who fulfilled all eligibility criteria for the CAIRO trial and therefore could have been included in this trial. Of the remaining 172 patients, 85 patients did not meet the trial eligibility criteria and 87 patients were not included in this analysis because of missing files. In 91 of the 224 eligible non-trial patients, the actual baseline performance status was not scored in the files, but was considered to be within the limits of the CAIRO inclusion criteria based on descriptive data in the patient files.

Reasons for non-participation of the 224 eligible non-trial patients were patient refusal (47 patients), treatment in non-participating hospital (50), logistical reasons (13), possible metastasectomy considered (8) and unknown (106). Reasons for non-eligibility in 85 patients were (more than one reason possible per patient): poor performance status (44), serious comorbidity (16), laboratory abnormalities (12), second malignancy in the past 5 years (10), no evaluable disease parameter (7), CNS metastases (3), and other reasons (12).

Outcome of trial versus non-trial patients
Baseline characteristics of the 224 non-trial patients who fulfilled all eligibility criteria of the CAIRO trial were comparable to the 394 eligible trial patients (Table 1). The 85 ineligible non-trial patients had a significantly worse performance status, more often an increased alkaline phosphatase and less often had a resection of their primary tumour.
First-line treatment of the 224 eligible non-trial patients consisted of fluoropyrimidine monotherapy in 130 patients (58%) and combination chemotherapy in 94 patients (42%). By randomisation this was 50%-50% in the CAIRO trial. Eligible non-trial patients receiving first-line monotherapy were significantly older compared with patients receiving first-line combination therapy, with a mean age of 64 versus 58 years, respectively ($p<0.0001$). There was no difference in the number of cycles in first line treatment between the eligible non-trial patients (7.2 (95 %CI 6.2-8.2) and trial patients (7.8, (95 %CI 7.2-8.4). None of the patients received bevacizumab or epidermal growth factor receptor antibodies in first-line treatment since these drugs were not yet available during the study period.

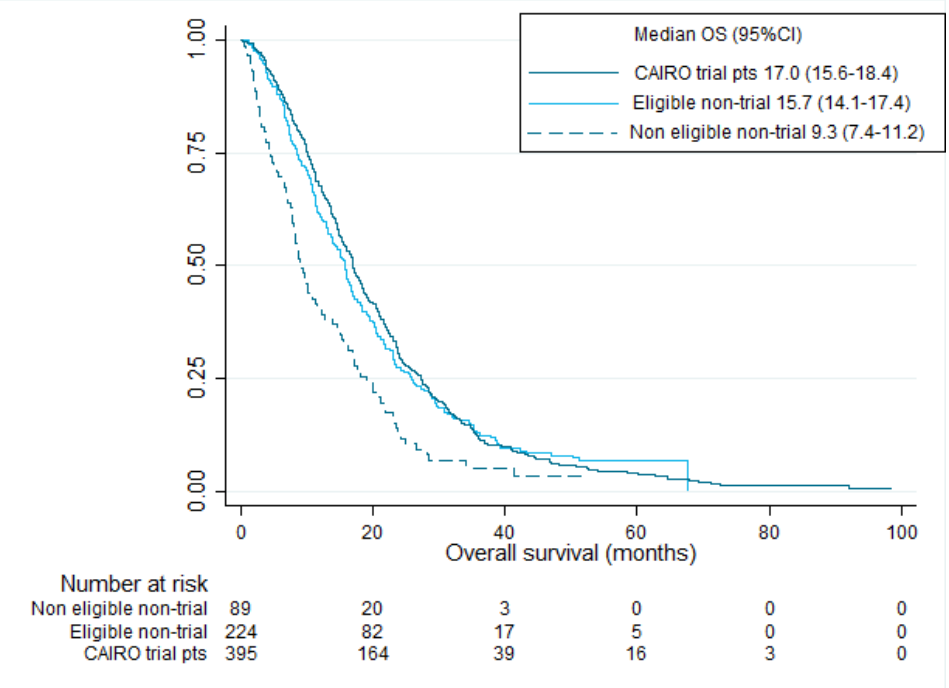


Figure 2: Overall survival for stage IV colorectal cancer patients participating to the CAIRO trial (n = 394), and patients who were treated outside trials and did (n = 224) or did not (n = 85) meet CAIRO eligibility criteria.

The median overall survival of eligible stage IV non-trial patients and stage IV trial patients was 15.7 months and 17.0 months from the date of diagnosis, respectively (p=0.7, HR 1.03, 95% CI(0.87-1.23) (Figure2). Median overall survival of ineligible non-trial patients was 9.3 months, which was significantly worse when compared to trial patients (p <0.01, HR 1.70, 95% CI 1.33-2.17). Median overall survival of patients not receiving any chemotherapy (n=2254) was 4.5 months (95% CI 4.1-4.9). The median age in this patient group was significantly higher (72 years, range 29-96). In a Cox proportional Hazards model with WHO performance status, number of metastatic sites, resection of the primary tumour, location of the primary tumour, serum LDH, and serum alkaline phosphatase, we did not observe a significant difference in overall survival between eligible non-trial and trial patients (HR 1.1, 95 % CI 0.98-1.25).

Trial participation
With 1946 non-trial stage IV colorectal cancer patients treated with chemotherapy identified during the trial accrual period and 394 stage IV patients actually included in the trial, the trial participation to the CAIRO trial was 20%. In addition, 30 patients were treated during the same period in trials other than CAIRO. Thus, overall trial participation during this period for stage IV cancer patients was 22%. When all diagnosed stage IV patients were considered the overall trial participation was 10%.

Discussion

We have compared the outcome in terms of overall survival between metastatic colorectal cancer patients treated within the scope of a clinical trial and patients treated outside this trial during the same period. A large Dutch multicentre phase III randomized trial (CAIRO) in metastatic colorectal cancer was used as the reference trial, which was performed within the framework of a cooperative group (DCCG) in approximately 80% of Dutch hospitals. In this trial the standard cytotoxic drugs for metastatic colorectal cancer were used at their normal doses and schedules, and standard entry criteria were used that are also applicable to the safe use of these drugs in daily practice. Moreover both arms of the trial were used in daily practice already. This use of standard treatments in both arms provided the opportunity to compare the outcome of trial patients with non-trial patients who were treated during the trial accrual period.
We observed no difference in median overall survival between trial and non-trial patients when non-trial patients were selected by trial eligibility criteria, but we found a significantly reduced overall survival in non-trial patients who did not meet these eligibility criteria. Several comments should be made on this result.
Our analysis is restricted to patients with stage IV (i.e. synchronous) metastases, since the NCR only registers patients at primary diagnosis. Previously published data from the CAIRO study have shown a comparable survival for patients with synchronous as compared to patients with metachronous metastases, when only synchronous metastatic patients were considered in whom a resection of the primary tumour was performed [8]. In a subsequent study we provided arguments that the worse prognosis that is generally reported for synchronous metastatic patients may be attributed to the fact that in many of these patients a resection of the primary tumour is not performed [9]. This may explain the shorter median overall survival of the patients in this study as compared to the median survival in more unselected patients with both synchronous and metachronous metastases treated with chemotherapy. Since a significantly smaller percentage of non-eligible non-trial

patients had their primary tumour resected, this could have contributed to their worse outcome (table 1). However, since the absolute difference was relatively small, we do not consider this factor to be the only reason for the worse outcome of these patients. The worse PS of the non-eligible non-trial patients may also have been a relevant factor. In any case, the prognostic value of resection of the primary tumour has not been firmly established and is currently the subject of ongoing prospective phase III studies such as the CAIRO4 trial.

Because of the straightforward design and the use of standard drugs for this indication, the conduct of the trial was easily feasible in all Dutch hospitals, and patient referral to specialized centres was therefore not required. Incentives such as access to experimental drugs with promising activity or high investigator fees were not applicable in this trial. Reasons for non-participation were retrospectively checked in the selected patient population, but it appeared that these data were not recorded in the files of the majority of patients.

Several factors have been described that could influence whether a trial in comparison with daily care may have a positive or a negative effect on the outcome of patients [3]. A possible trial effect was hypothesised to be attributed to five possible factors: the therapy, the protocol, the care, the Hawthorne effect and a placebo effect. The authors of this systematic review concluded that, although the evidence was not conclusive and the available data were limited, it is more likely that participation in a clinical trial had a positive effect. The effect appeared largest in trials in which an already established and effective treatment was applied. However, given the fact that standard drugs and schedules were administered in both treatment arms of the CAIRO trial we do not believe that such an effect is present in our analysis. Neither can differences in care or placebo effect be considered as important factors to improve the outcome of this trial in comparison with daily practice. Other factors such as patient age, geographical and social barriers on clinical trial accrual have been described [10,11], but we did not investigate these factors in our study.

The external validity of trial results has previously been a matter of concern [12]. However, the external validity of this trial is further supported by the fact that eligible patients in the trial and outside the trial together represented almost 70 % of the stage IV patients receiving chemotherapy as identified by the NCR during the trial accrual period.

The CAIRO trial eligibility criteria involved no restrictions other than related to the safe use of standard chemotherapeutic drugs. Our finding of a significantly reduced overall survival in non-trial stage IV colorectal cancer patients who did not meet the trial eligibility criteria is a strong argument for the strict use of these criteria in general practice. Studies on the outcome of treatments in general practice, which are often initiated by healthcare authorities on (usually

expensive) drugs, should therefore always evaluate whether patients did meet the standard eligibility criteria for these drugs. The worse outcome of non-trial versus trial patients that have been reported by others [13] is most likely due to the fact that many non-trial patients did not meet the trial eligibility criteria. The large group of patients who did not receive any chemotherapy had a poor median survival of 4.5 months. This group was significantly older compared to the trial patients. Older patients are frequently underrepresented in cancer clinical trials [11]. However, many colorectal cancer trials have shown that age by itself does not indicate a worse outcome of systemic treatment [14]. The main outcome of our study is that trial results can only be expected in the general population if the same selection criteria are applied.

Lastly, the CAIRO trial had a high participation rate of 20%. We consider it unlikely that trial participation rates differ between patients with synchronous and metachronous metastatic colorectal cancer. Our trial participation rate exceeds the commonly reported 5-14% in cancer trials [15], although these latter findings were not always restricted to patients actually receiving treatment as in our analysis. In a more selected population study a participation rate of 30 % [13] has been reported, which shows the possibility of a high participation rate in hospitals in which a protocol is available for the majority of patients. The simple and straightforward design of the CAIRO trial, its use of standard drugs and the clinically relevant study objective will likely have had a positive effect on trial participation.
In conclusion, for stage IV colorectal cancer patients we did not demonstrate a difference in outcome between patients included in a clinical trial and patients treated during the same period outside that trial but who met the trial eligibility criteria. Patients treated outside the trial not meeting the eligibility criteria had a significantly worse outcome. These results strongly indicate that the external validity of trial results only applies when trial eligibility criteria are respected in general practice. This also implies that for patient groups not fulfilling the safety criteria of trials in which the efficacy of a certain drug regimen was demonstrated, the treatment results should be monitored and compared to the patient groups with the same characteristics not receiving the study drug (preferably in a randomised trial) in order to assess the risks and benefits of the drug regimen in these selected groups. Such policy may in the end reduce the costs of healthcare.

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Chapter 3b

Letter Re: Generalizability of trial results to elderly medicare patients with advanced solid tumors

JNCI 2015 Jun;107(6):djv104

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3b

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Re: Generalizability of trial results to elderly medicare patients with advanced solid tumors

With interest we have read the analysis of Dr. Lamont and colleagues on three chemotherapy regimens in two different settings, clinical trials vs usual care (17). Using SEER-Medicare data the authors conclude that clinical trials for advanced pancreatic cancer and lung cancers tended to correctly estimate survival for Medicare patients aged 65 to 74 years, but to overestimate survival for older Medicare patients. However, the authors did not check the eligibility of patients for the treatments administered. We have analysed this aspect, and found that this may statistically significantly impact the outcome of treatment. We compared the outcome of 394 metastatic colorectal cancer patients treated with standard cytotoxic drugs within a prospective phase 3 trial using standard safety eligibility criteria (18) versus 309 patients treated outside the scope of this trial but with the same drugs and during the trial accrual period (19). Patients treated outside the trial were divided into 2 groups: patients who would have qualified for trial participation (n=224), and patients who failed to meet relevant eligibility criteria(n=85). We found that the outcome of patients treated outside the trial but who could have qualified was comparable with the outcome of patients treated within the trial, 15.7 months and 17.0 months respectively (two-sided log-rank test, p=0.70; HR=1.03, 95%CI=0.87-1.23). However, the outcome of patients treated outside the trial who did not meet standard eligibility criteria was statistically significantly lower compared to eligible non-trial patients and trial patients, with median overall survival times of 9.3 months(95%CI=7.4-11.2), 15.7 months(95%CI=14.1-17.4), and 17.0 months (95%CI=15.7-18.4), respectively ($p<0.01$, two sided log-rank test), figure 1. There was no statistically significant difference in age between these groups, 61 years for the eligible non-trial patients, 61 years for the trial patients and 63 for the non-eligible non-trial patients (p=0.28). We concluded that the external validity of trial results only applies when trial eligibility criteria are respected in general practice. Therefore, the finding of Lamont et al. (1) that trial results are not generalizable in the older patient population may possibly be explained by the fact that these patients are not eligible for trials on criteria other than age. We strongly recommend to include the assessment of standard baseline safety criteria in population-based studies on the outcome of systemic treatments in cancer patients in daily practice.

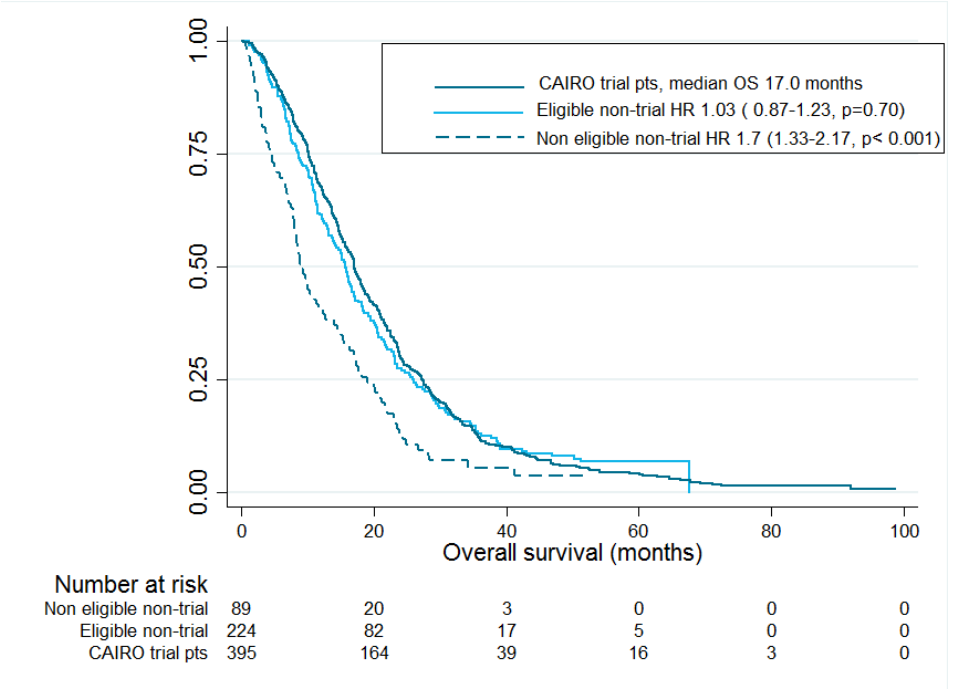

Figure 1 Overall survival for stage IV colorectal cancer patients participating in the CApecitabineIrinotecanOxaliplatin (CAIRO) trial and patients who were treated outside trials and did or did not meet CAIRO eligibility criteria (two-sided log-rank test).

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Chapter 4

The prognostic value of WHO performance status in relation to Quality of Life in advanced colorectal cancer patients

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4

Abstract

Introduction
Performance status (PS) is an established prognostic factor in patients with advanced cancer, and is usually scored by the treating physician. The EORTC QLQ-C30 questionnaire as reported by cancer patients is a validated tool to assess quality of life(QoL). Subjectivity plays a role in both assessments, and data on a direct comparison are scarce.

Methods
We compared the prognostic value for overall survival (OS) of the WHO PS to the baseline physical function scale of the EORTC QLQ-C30 (QLQ-C30PF) in a prospective randomised phase 3 trial in metastatic colorectal cancer, the CAIRO study. Patients were divided into 2 groups based on the baseline QLQ-C30PF. QLQ-C30PF was considered "good" if the score was more than 66.7% and "poor" if 66.7% or less. Results were validated in a subsequent phase 3 study in mCRC, the CAIRO2 study.

Results
The median OS for patients with a "good" QLQ-C30PF and a "poor" PF in patients with WHO PS 0, was 20.3 months (n=300) and 10.4 months (n=44), in patients with WHO PS 1 16.8 months (n=125) and 10.1 months (n=63), and in patients with WHO PS 2 16.2 months (n=11) and 9.9 months (n=12), respectively. In a Cox regression model which included other prognostic factors, "good" versus "poor" QLQ-C30PF was significantly prognostic for overall survival (0.57 95%CI 0.46-0.72), but not WHO PS. These results were confirmed in the CAIRO2 study.

Conclusions
We demonstrate in mCRC patients that PF, as assessed by patients using the EORTC QLQ C-30, is superior in terms of prognostic value to WHO PS as scored by physicians. Our data support to include the results of baseline EORTC QLQ-C30PF instead of WHO PS as a stratification parameter in oncology trials.

Introduction

Assessment of the performance status (PS) is an important tool for physicians to evaluate physical functioning of patients. In clinical oncology it is widely used to decide which patients are physically suitable for treatment. It is an established prognostic factor for survival (20), and therefore frequently used as a stratification parameter in randomised clinical trials. Various scoring systems of PS are used: Karnofsky introduced the first performance score in 1948 (21). In 1960 the Eastern Co-operative Oncology Group(ECOG) PS scale was introduced(22), which is more simple and has a better predictive validity (23). This was later adapted to a scale of 6 points, which is currently known as the ECOG PS or WHO PS score. Obviously, subjective factors may play a role in the assessment of the PS of the patient by the physician, and the quality of this assessment may vary(20).

The current standard of patient-centred care has resulted in more attention to Patient Reported Outcomes (PROs). These PROs are increasingly considered as important measures to assess the effects of treatment in terms of toxicity and well being as compared to outcome as assessed by physicians(24). The prognostic value of PROs has recently been studied in several tumour types (25-27). The quality of life (QoL) questionnaire (QLQ) C30 of the EORTC is one of the most frequently used questionnaires to assess PRO in oncology clinical trials. The QLQ-C30 is divided in global health status/QoL, functional scales and symptom scales items.

A cross-validation of the Karnofsky PS and the QLQ-C30 (28) showed that Karnofsky PS only reflects physical functioning, whereas the QLQ-C30 reflects a greater scope of physical functioning by also including the symptoms of pain, breathing and fatigue as well as non-physical functioning concerning social, emotional, and cognitive well-being. In the phase 3 CAIRO study of the Dutch Colorectal Cancer Group (DCCG) (18) in patients with advanced colorectal cancer (ACC) we noted a discrepancy within several patients between the specific physical functioning scores of the QLQ-C30 (QLQ-C30PF) as reported by patients and the WHO PS as scored by physicians, while these items in principle should have a similar result.

We therefore performed an overall comparison on the prognostic value in terms of overall survival (OS) between the WHO PS as assessed by the treating physicians and the baseline QLQ-C30 PF as reported by patients. We then validated our results in a subsequent phase 3 study in mCRC, the CAIRO2 study(5).

Materials and methods

Study design
We retrospectively compared the prognostic value for median OS of the WHO PS as reported by the treating physicians with the QLQ-C30PF as reported by patients.

Patient population
Metastatic colorectal cancer patients who participated in the randomised phase 3 CAIRO trial were used for this analysis, Clinical Trials.gov NCT00312000(18). In this trial, 820 previously untreated mCRC patients were randomised between 2 arms: 1) sequential treatment with capecitabine, irinotecan, and capecitabine plus oxaliplatin, and 2) upfront combination treatment with capecitabine plus irinotecan followed by capecitabine plus oxaliplatin. Stratification parameters included WHO PS (0-1 versus 2), prior adjuvant treatment (yes versus no), serum LDH value (normal versus abnormal), predominant localisation of metastases (liver versus extrahepatic), and treatment centre. The primary endpoint was OS, secondary endpoints included QoL. The final results did not show a significant difference in median OS between the two treatment arms. QoL evaluation was a prospective part of the study, which for financial reasons was limited to the first 635 patients that were included in the study. All patients who completed a baseline QoL questionnaire were included in this analysis.
We validated our results in the CAIRO2 study, in which the addition of cetuximab to a regimen of capecitabine, oxaliplatin and bevacizumab was investigated in mCRC patients , Clinical trials.gov NCT00208546(5). CAIRO2 included patients with WHO PS 0-1, and baseline QLQ-C30 was also a prospective part of the study.

Measures
Both CAIRO and CAIRO2 study required the assessment of WHO PS by the treating physician of all patients prior to randomisation (Table 1). Patients were asked to complete the baseline EORTC QLQ-C30(29) questionnaire prior to randomization and every 3 cycles thereafter until disease progression. For the current analysis we used the baseline scores of the answers to the 5 questions of the QLQ-C30 PF (Table 2). Other scores of the QLQ-C30 were not analysed. We classified patients as having poor physical functioning when 3 or more questions were answered with “quite a bit” or “very much”. Patients who did not meet this criterion were classified as having good physical functioning. With the formula of the EORTC QLQ-C30 PF scores were calculated according to the EORTC QLQ-C30 manual(30). By this calculation a good score should then be more than 66.7% and a poor score 66.7% or less. The scores of the physical

functioning were then used to divide patients for each of the 3 WHO PS groups (0, 1 and 2) into two groups: those with either “good” or “poor” QoL PF, resulting in a total of 6 groups.

Statistics

OS was estimated using the Kaplan-Meier method and was compared using the log-rank test. All tests were 2-sided with an alpha of 5 %. A multivariable Cox-regression model was used to test which scoring system had a better prognostic value, WHO PS or QLQ-C30PF. The other variables entered in this model were the factors that were found prognostic in the retrospective analysis of the CAIRO study: serum LDH (normal vs elevated), number of metastatic sites (1 vs more than 1), resection of the primary tumour, and treatment arm (18, 31).
The same method and analysis was performed in the CAIRO2 trial. All analyses were performed using STATA 13.1.

WHO Performance Status	
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 1. WHO Performance status

	EORTC QLQ-C30 (version 3.0.)	Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

Table 2. Physical functioning items of the EORTC QLQ-C30

Results

A total of 556 patients included in the CAIRO trial completed a baseline QoL form. One patient had to many PF items missing therefore 555 patients were eligible for this analysis. Patients with WHO PS 0, 1 and 2 had a median OS of 18.9, 14.7, and 12.9 months, respectively (p<0.001, Fig. 1). Patients with "good" and "poor" QLQ-C30PF had a median OS of 19.3 and 10.2 months, respectively (p<0.001, Fig. 2). Next, we combined the results of WHO PS and QoL scores (Table 3). The median OS for patients with a "good" versus a "poor" QLQ-C30PF of patients with a WHO PS 0 was 20.3 months (n=300) and 10.4 months (n=44), respectively. For patients with WHO PS 1, this was16.1 months (n=126) and 10.1 months (n=63), respectively, and for patients with WHO 2 16.2 months (n=11) and 9.9 months (n=12)respectively (Table 3, Fig 3).

In a multivariable Cox regression model which included baseline serum LDH, number of metastatic sites, resection status of the primary tumour and treatment arm, a "good" versus "poor" QLQ-C30 PF score was significantly prognostic for OS (HR 0.57 (95%CI 0.46-0.72) as was serum LDH with a HR of 0.56 (95%CI 0.46-0.67), but not WHO PS (WHO PS 0 vs 1 HR 0.85, 95%CI 0.69-1.02; WHO PS 0 vs 2 HR 0.87, 95%CI 0.54-1.39, Table 4).

WHO PS	QLQ-C30 PF	Total N (%)	Median OS (months)	95% Confidence Interval	
				Lower Bound	Upper Bound
0	Good QoL	300 (54%)	20.3	18.2	21.9
	Poor QoL	44 (8 %)	10.4	6.5	17.1
1	Good QoL	125 (23 %)	16.8	14.0	19.8
	Poor QoL	63 (11 %)	10.1	6.6	12.2
2	Good QoL	11 (2 %)	16.2	4.6	23.1
	Poor QoL	12 (2 %)	9.9	3.6	22.2

Table 3 Overall survival for patients with good versus poor QoL within the subcategories of patients with WHO 0 ,1, and 2.

Variables	HR	95 % CI	p-value
Serum LDH normal vs elevated	0.56	0.46-0.67	0.000
QLQ-C30PF good vs poor	0.57	0.46-0.72	0.000
Number of metastatic sites 1 vs >1	0.72	0.61-0.87	0.001
WHO PS 0 vs 1	0.85	0.69-1.0.2	0.09
0 vs 2	0.87	0. 54-1.39	0.56
Resection primary tumour (yes vs no)	0.76	0.61-0.95	0.02
Treatment arm (sequential vs combination chemotherapy)	0.92	0.77-1.1	0.36

Table 4 Multivariable Cox regression model for overall survival

In the CAIRO2 trial 699 of the 755 randomised patients completed a baseline QoL form. Patients with WHO PS 0 and 1 had a median OS of 22.2 and 17.1 months, respectively (p=0.004). Patients with "good" and "poor" QLQ-C30PF had a median OS of 22.0 and 15.2 months, respectively (p < 0.001). The median OS of patients with a "good" versus a "poor" QLQ-C30PF in the group of patients with WHO PS 0 was 23.5 months (n=377) and 18.9 months (n=183), respectively, and in the group of patients with WHO PS 1 17,1 months (n=61), and 14.2 months (n=78), respectively (Table 5.). In a multivariable Cox regression model which included the same variables as in the CAIRO analysis, a "good" versus "poor" physical functioning was significantly prognostic for OS (HR 0.68 (95%CI 0.55-0.84), but not WHO PS (WHO PS 0 vs 1 HR 0.89, 95%CI 0.74-1.07, Table 6).

WHO PS	QLQ-C30PF	Total N	Median OS months	95% Confidence Interval	
				Lower Bound	Upper Bound
0	Good	377 (54 %)	23.5	21.7	25.9
	Poor	61 (9 %)	17.1	12.0	22.0
1	Good	183 (26 %)	18.9	16.4	21.3
	Poor	78 (11 %)	14.2	10.9	17.4

Table 5 Overall survival for patients with good versus poor QoL within the subcategories of patients with WHO 0 and 1 in the CAIRO2 study

Variables	HR	95 % CI	p-value
Serum LDH normal vs elevated	0.68	0.57-0.81	0.001
QoL good vs poor	0.68	0.55-0.84	0.000
Number of metastatic sites 1 vs >1	0.72	0.59-0.87	0.001
WHO PS 0 vs 1	0.89	0.74-1.07	0.21
Resection primary tumour (yes vs no)	0.80	0.64-1.00	0.05
Treatment arm (CB vs CBC)	0.85	0.72-1.01	0.074

Table 6 Multivariable Cox regression model for overall survival in the CAIRO2 study

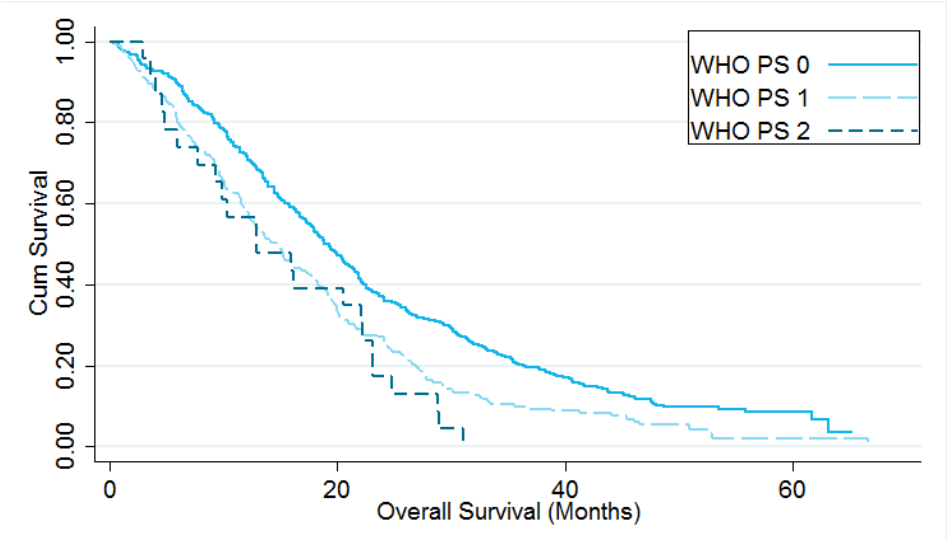

Figure 1: Overall survival for WHO PS 0 (median 18,9 months, 95% CI 17,3-21.0,7), 1 (median 14,7 months, 95% CI 12,2-17,3) and 2 (median 12,9 months(95% CI 4,2-21,6)

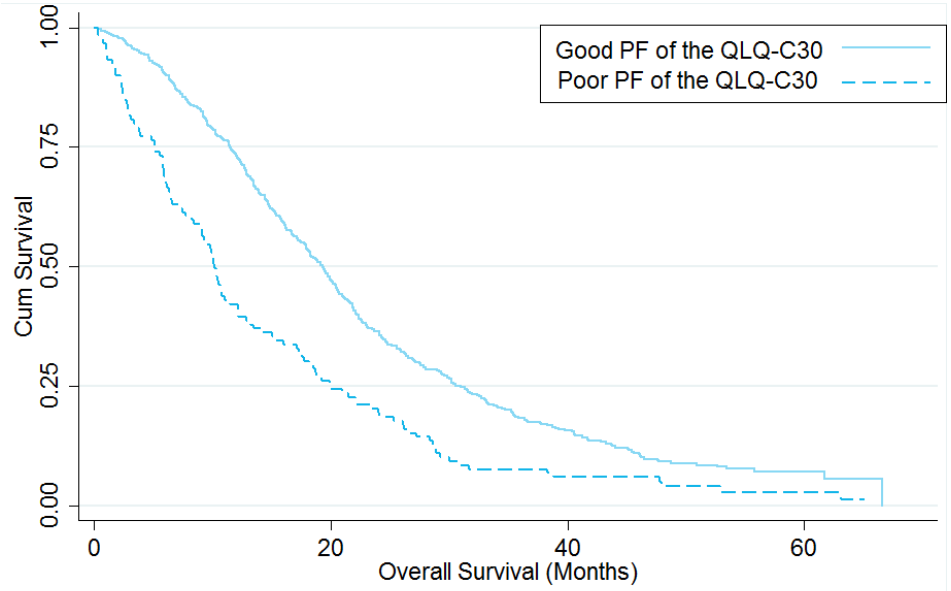

Figure 2 Overall survival for 'good' QoL (median 19,3 months, 95% CI 17.9-20.5)vs 'poor' QoL (median 10.2 months, 95%CI 8.5 12.2).

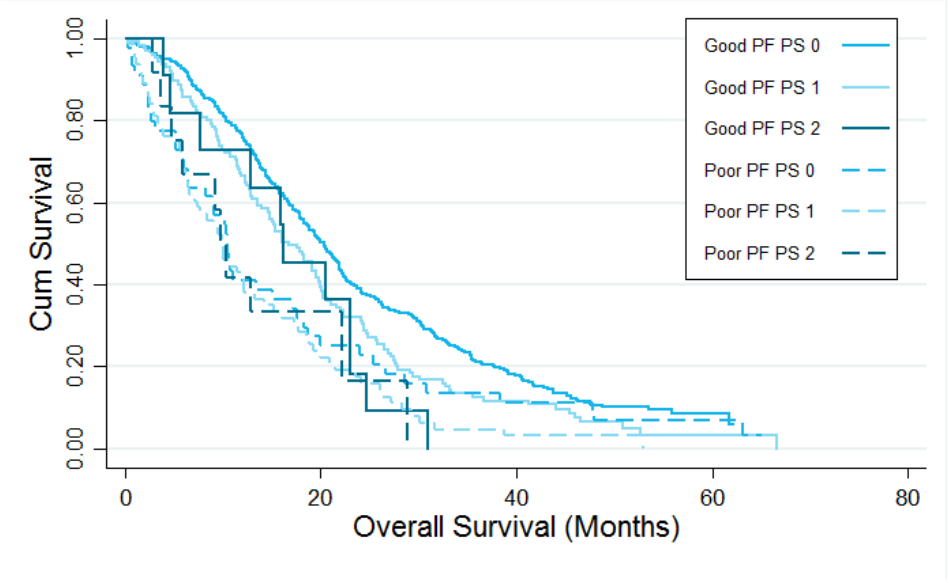

Figure 3. Overall survival of WHO PS and 'good' QoL vs 'poor' QoL.

Discussion

The CAIRO study investigated the optimal use of standard chemotherapy regimens in patients with mCRC. During the analysis of the data from this study, we sometimes observed a discrepancy between the WHO PS as scored by physicians and the 5 physical functioning items from the EORTC QLQ-C30 as scored by patients. For example, a patient with a WHO PS score of 0 reported that he had quite a bit trouble taking a short walk. Therefore we performed an overall comparison of physician- versus patient-reported physical performance in relation to the median OS. Although WHO PS and QLQ-C30PF each showed a significant difference in median OS between their respective subgroups, QLQ-C30PF but not WHO PS was a significant prognostic factor in multivariable analysis. These results were confirmed in the CAIRO2 study.

The clinical relevance of this finding is that within each category of patients with WHO PS 0, 1 and 2, a large difference in median OS was observed between patients with a good and a poor QLQ-C30 PF. For instance, 13% of patients (44 out of 344) with a WHO PS score of 0 had a poor QLQ-C30PF, and had a worse survival as compared to the 66% of WHO PS 1 patients with good QLQ-C30PF. QLQ-C30 PF was also a relevant discriminating factor within the group of patients with PS1 and PS2, although within the latter category the number of patients was small. Therefore, our results show a better prognostic value for PRO concerning physical functioning as measured by the physical functioning scale of the EORTC QLQ-C30 compared to the physician-rated WHO PS. Patients with both WHO PS 0 or 1 and good QLQ-C30 PF had the best survival, while patients with a WHO PS 0 but a poor QLQ-C30 PF had comparable survival to patients with a WHO PS 2. The prognostic value of serum LDH was comparable to QLQ-C30 PF 0, with a HR of 0.56 (95%CI 0.46-0.67). We have confirmed these results in the CAIRO2 study for patients with WHO PS 0 and 1 by multivariable analysis.

PROs were found to be prognostic in several other studies (27, 32-35). Gotay et al. systematically assessed the impact of various PROs on patient survival in 39 clinical trials in different tumour types and concluded that PROs might be considered for stratification purposes in future trials, as they were often better predictors of survival than PS. Quinten et al. (27) assessed prognostic significance of socio-demographic and clinical variables and the QLQ-C30 with Cox proportional hazard models in a meta-analysis of 30 different trials also in different tumour types. They found physical functioning, pain and appetite loss to be prognostic in addition to socio-demographic and clinical measures. Efficace et al. (26) showed that social functioning as measured by the social functioning scale of the EORTC QLQ C-30, acted as an important prognostic measure for survival beyond a number of previously known biomedical parameters in metastatic colorectal cancer(26). Since we analysed the

prognostic value of physician versus patient assessed physical performance, we only used the questions of the physical functioning part of the QoL-C30, because we considered these questions as the best surrogate for WHO PS.
An important limitation of scoring PS and QLQ-C30 PF remains their subjective nature, which may occur at the side of both the physician and the patient. Blagden et al. studied the agreement in assessment of the ECOG performance status among patients and their physicians (36). Physicians were more likely to assign a better score to patients than patients did to themselves. This was confirmed by Schnadig et al.(37). However, these subjective parameters can be validated by objective outcome measures such as OS. Although we and others show that PS assessed by patients and physicians is significantly associated with survival, our data strongly support the superiority of patient-reported baseline QoL to physician-assessed WHO PS.
In conclusion, physical functioning as assessed by patients using the EORTC QLQ C-30PF is more prognostic than WHO PS as scored by physicians. Our data suggest to include the results of baseline physical functioning of the EORTC QLQ C 30 PF instead of WHO PS as a stratification parameter in oncology trials.

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Chapter 5

Clinical Trial Performance in Metastatic Colorectal Cancer: an Evaluation of Participating Centers in the CAIRO studies of the Dutch Colorectal Cancer Group.

Submitted

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Abstract

Background.
High quality clinical trials are essential for further improvement of treatment strategies for prolonged survival and reliable evidence-based outcomes. However, there are no defined standards for the quality of clinical trial performance. The aim of this study is to examine and compare clinical trial performance with a composite score between (different types of) hospitals, to identify potentially predicting factors for a high trial performance and examine a learning curve in composite performance scores between early compared to subsequent included patients.

Methods.
We evaluated trial performance in three large phase 3 randomized clinical trials in metastatic colorectal cancer (CAIRO studies of the Dutch Colorectal Cancer Group, total n=2131) with a newly introduced composite score, consisting of stratification errors, major protocol violations, number of included ineligible patients, and reporting of serious adverse events (SAE) on hospital and patient level. These data were supplemented with a hospital survey containing questions about number of beds, oncologists and research nurses. Composite scores were compared between early (first 3 patients) and subsequent patients. A logistic regression was performed to identify factors associated with better trial performance (3-4 points).

Results.
We observed variation in trial performance between 84 participating hospitals. However, no differences in performance between hospital categories (university, teaching, regional hospitals) were identified and none of the examined variables could be linked to a high composite performance score. In top 10 ranking hospitals with highest inclusion rates, trial performance on patient level was significantly lower in the first three inclusions compared to subsequent patients.

Conclusions.
Trial performance was comparable between different types of hospitals and no factors were able to predict a high composite trial performance score. In the highest including hospitals we identified a learning curve for trial performance. We therefore recommend increased support during the first patient inclusions in participating centers in order to improve trial performance. Our composite score could be used as a quality metric for trial performance for individually based hospital evaluation.

Introduction

Survival in metastatic colorectal cancer has improved substantially over time, which is for a large part due to the availability of more effective systemic therapies.(38, 39) Clinical trials are essential in this process, and will be necessary for further improvement of treatment. Maintaining high quality within these trials is a requisite for reliable evidence-based outcomes. However, even in the presence of guidelines for the standard of care, there are no defined standards for the quality of clinical trial performance.

Quality assurance of clinical trials is a complex issue. Several factors contributing to a good performance can be identified [13], such as the requirement for adequate methodology and protocols in order to maintain reliability and validity of the obtained results. However, data on the level of protocol adherence are scarce. Multi-centre trials , especially if they are complex, may lead to variability in treatment and data collection. To prevent biased results and to maintain integrity of the data, trial protocols need to be followed as closely as possible. Quality assurance is therefore a prerequisite.

Although no validated indicators for clinical trial performance are available, a potentially useful criterion for clinical trial adherence may be the number of protocol deviations or protocol violations. Protocol deviations are not caused or preventable by the investigator, in contrast to protocol violations. Therefore, the number of protocol violations may be used to assess and compare (investigator) trial performance.[40] Major protocol violations are defined as deviations, which may result in harm to the patient and may impact the integrity of data. These violations may have major impact on data interpretation and may result in the assumption of wrong recommendations.[40, 41] Protocol violations are usually underreported and differs widely among studies.[41]

The number of study participants included per participating hospital in multicenter trials is earlier suggested as a potential indicator of trial performance.[42] However, this finding prompted several comments that agreed[43, 44] and disagreed with this indicator[45, 46]. Also conflicting results regarding trial performance between different types of hospitals have been reported.[42, 47, 48] In case of any reported difference in performance, there are no data on the underlying contributing causes. Therefore, the aims of our study are: 1) to examine clinical trial performance of hospitals that participated to national phase 3 studies in metastatic colorectal cancer using a scoring system based on stratification errors, major protocol violations, serious adverse event (SAE) reporting and the number of ineligible patients that was included; 2) to

identify factors that may explain differences, if any, in clinical performance between different hospital categories; 3) to compare clinical trial performance between hospitals with low and with high accrual rates; and 4) to examine whether a learning curve can be identified per hospital between early included patients compared to subsequent included patients in the trial.

Methods

Data from three large phase 3 randomized clinical trials in metastatic colorectal cancer were pooled for this study: CAIRO [NCT00312000][4], CAIRO2 [NCT00208546][5], and CAIRO3 [NCT00442637][6]. The Dutch Colorectal Cancer Group (DCCG) was the sponsor of all studies, and a total of 84 hospitals participated. Of the participating hospitals 43 (51%) were regional hospitals, 32 (38%) teaching hospitals, 8 (10%) university hospitals, and 1 cancer institute. We have added the latter to the university hospitals group in all analyses. For all 3 studies, regional initiation meetings were organized, and accrual was only allowed in hospitals of which relevant staff had been present at these meetings.

The primary outcome of our study was trial performance, consisting of a composite of 4 dichotomous items: 1) number of errors during stratification (cut-off 10%); 2) number of major protocol violations (cut-off 10%); 3) number of included ineligibles (cut-off 5%), and 4) reported serious adverse events (SAE) within 7 days (cut-off 75%). For all 4 items a participating hospital could gain 1 point: the composite score ranges between 0 and 4 per participating hospital per study. A higher score indicates a better trial performance. The cut-off scores are based on relevance for clinical practice: therefore the cut-off value for ineligibles is for example lower than the cut-off value for stratification errors, as ineligibility is expected to be more harmful than a stratification error. All data regarding the primary outcome were collected prospectively during the trials. To compare hospitals with low and high accrual rates, scores were compared for sites with low (less than 5 patients) and high (5 or more patients) accrual. To identify variations in trial performance between early and later patient inclusions per hospital (learning curve), we labeled the first 3 included patients in the top-10 hospitals with highest inclusion rates as ‘early included’ and subsequent patients as ‘later included’. An adjusted composite score of 3 dichotomous items (stratification errors, major protocol violations and ineligibility) was calculated at patient level, SAE reporting was excluded since SAE’s may occur at any time during the course of the study and therefore may not be a valid measurement to identify a learning curve.
A questionnaire was sent to local investigators of participating hospitals to the CAIRO3 study during its conduct (March 2008), which consisted of the following items, which were to be scored per hospital: the number of beds, the full-time

equivalence (FTE) of medical oncologists, the number of hours per week of a research nurse and the number of newly diagnosed patients with colorectal cancer per year.
Data from the questionnaires were entered into an electronic database and merged with the data of the primary outcome per participating hospital per study. Characteristics of participating hospitals were compared between the three categories of hospitals. Categorical variables were analyzed using chi-squared testing, or fisher's exact test if appropriate. Continuous variables were compared between groups Kruskall-Wallis analysis. The primary outcome and its individual components were tested against the three hospital categories using a chi-squared test. An univariable en multivariable logistic regression analysis was performed to identify factors associated with a higher composite performance score and additionally univariable logistic regression was performed on the individual components of the composite score. All analyses were performed for all 3 trials combined as well as for each individual trial. All tests were two-sided and a p-value of <0.05 was considered to be statistically significant.

Results

Overall, 84 Dutch hospitals participated in one or more CAIRO studies. A total of 66 hospitals participated in the CAIRO study (total included patients; n=820), 73 hospitals in the CAIRO2 study (n=755), and 61 hospitals in the CAIRO3 study (n=556). The response rate to the questionnaire was 45% (38/84). The characteristics of participating hospitals are shown in Table 1.

The median inclusion of patients was significantly different between categories of hospitals in the total dataset with a median inclusion of 12 patients in university hospitals, 11 in teaching hospitals and 7 in regional hospitals ($p <0.01$). Furthermore, in each study the median inclusion in university, teaching and regional hospitals was 14, 18 and 7 patients ($p <0.05$) in CAIRO, 12, 13 and 7 patients ($p < 0.05$) in CAIRO2, and 7, 7 and 8 patients in CAIRO3 ($p=0.91$), respectively (Table 1). The median overall composite performance score was 2 (IQR 2-3) which was not significantly different between categories of hospitals: university 2 (IQR 2-3), teaching 2 (IQR 1-3) and regional 2 (IQR 2-3). The median overall composite performance score was 3 (IQR 2-3) for hospitals including less than 5 patients, and 2 (IQR 1-3) for hospitals including 5 patients or more ($p <0.01$).
In Figure 1, the mean composite performance score is plotted against the median inclusion rates for the different types of hospitals for CAIRO, CAIRO2 and CAIRO3. In CAIRO and CAIRO2, the university hospitals had the highest score, but in the CAIRO3 study, regional hospitals scored highest. Twenty-one

hospitals that participated in at least 2 CAIRO studies, had a persisting low composite performance score (0-2 points). On the other hand, 6 hospitals had a persisting high performance score (3-4 points).
Table 2 describes the univariable and multivariable analysis for factors that are potentially associated with a high composite performance score (3-4 points). The following were associated with the outcome: FTE oncologist (OR 1.15 per additional FTE; 95% CI 1.01-1.31), hours of research nurse (OR 1.01 per additional hour; 95% CI 1.00-1.02) and number of included patients (OR 0.19 for ≥ 5 patients included; 95% CI 0.09-0.40). However, none of these variables remained significant after adjusting for all covariates listed in Table 2.

Variable		University hospitals	Teaching hospitals	Regional hospitals	p-value
Number of accruing hospitals	CAIRO	7	26	33	
	CAIRO2	9	31	33	
	CAIRO3	7	27	27	
Accrual per hospital					
CAIRO	Median (IQR)	14 (8-19)	18 (9-24)	7 (5-12)	<0.05
CAIRO2	Median (IQR)	12 (8-16)	13 (8-16)	7 (4-10)	<0.05
CAIRO3	Median (IQR)	7 (3-12)	7 (4-11)	8 (2-12)	0.91
Number of beds per hospital	Median (IQR)	882 (715-1200)	666 (480-930)	384 (314-486)	<0.05
Number of hours research nurse per week per hospital	Median (IQR)	45 (7-80)	16 (0-43)	3 (0-16)	0.18
Number of full-time oncologists per hospital	Median (IQR)	9 (6-16)	3 (2-4)	2 (2-2)	<0.05

Table 1. Characteristics of participating hospitals

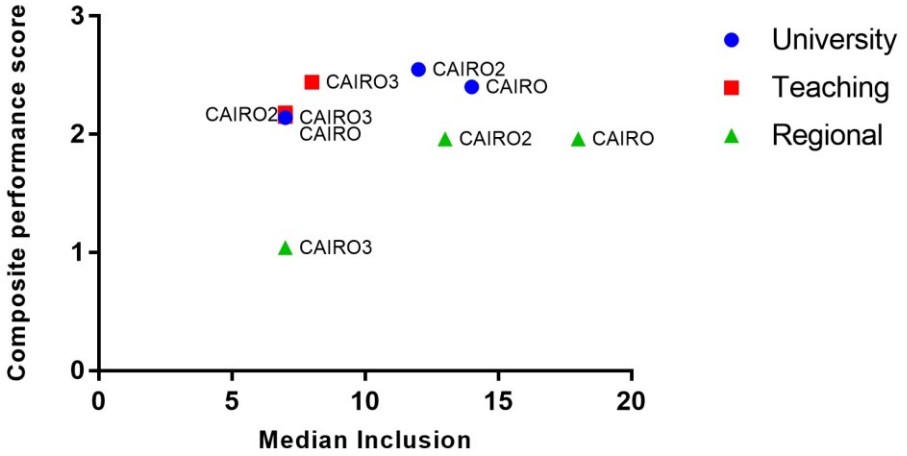

Figure 1. Mean composite performance score and the median inclusion for different types of hospitals in CAIRO, CAIRO2 and CAIRO3

None of the examined variables could be linked to the individual components of the composite score, except for low and high inclusion rates as expected, since hospitals with less than 5 inclusions had a higher mean overall composite score than hospitals including 5 patients or more. Odds ratios were 0.36 (95% CI 0.18-0.72) for SAE reporting, 0.43 (95% CI 0.19-0.99) for major protocol violations and 0.34 (0.16-0.69) for stratification errors, respectively.

The individualized patient composite scores in early included patients (first 3 inclusions) were significantly lower compared to subsequently included patients ($p < 0.05$). This learning curve was observed in the top-10 ranking hospitals with highest inclusion rates.

Variable		OR (95% CI) Unadjusted	OR (95% CI) Adjusted*
Hospital type	University	reference	reference
	Teaching	0.55 (0.21-1.39)	0.70 (0.07-6.67)
	Regional	0.60 (0.24-1.51)	1.39 (0.10-19.4)
Number of beds		1.00 (1.00-1.00)	1.00 (1.00-1.00)
FTE oncologist		1.15 (1.01-1.31)	1.15 (0.85-1.56)
Hours of research nurse		1.01 (1.00-1.02)	1.00 (0.98-1.02)
Number of new metastatic colorectal patients per year	11-20 patients	reference	reference
Number of new metastatic colorectal patients per year	21-30 patients	0.73 (0.24-2.19)	0.62 (0.16-2.37)
	31-40 patients	1.84 (0.51-6.70)	2.23 (0.49-10.2)
	41-50 patients	2.11 (0.35-12.6)	2.07 (0.17-25.5)
	>50 patients	0.84 (0.21-3.44)	0.57 (0.06-5.23)
Number of included patients (<5 or ≥ 5 patients)		0.19 (0.09-0.40)	0.35 (0.08-1.55)

Table 2. Unadjusted and adjusted odds ratios (OR) with 95% Confidence Intervals (CI) for a higher (3-4 points) composite performance score.
* adjusted for all variables listed.

Discussion

We studied clinical trial performance in three large randomized clinical trials investigating treatment strategies in metastatic colorectal cancer. Based on a composite trial performance score including stratification errors, major protocol violations, SAE reporting and inclusion of ineligible patients, we identified a large variation in trial performance between hospitals. Inclusion rates were significantly higher in university and teaching hospitals compared to regional hospitals. However, we did not find a significant difference in trial performance between hospitals categories. There were no hospital-based factors identified (number of beds, FTE oncologist, hours of research nurses available), that could explain differences between hospitals with high or lower trial performance. Interestingly, hospitals with a low inclusion rate had a higher mean composite score compared to hospitals with a high inclusion rate. In the top-10 hospitals with highest inclusion rates, we observed a learning curve for trial performance.

Our results are in line with earlier work by Begg et al.(47) They studied trial performance by rates of ineligibility, compliance with the protocol, and submission of data and concluded that the quality of participation of different types of hospitals was comparable. In agreement with their results, we observed no differences between type of hospitals using a composite endpoint that also included SAE reporting. However, we did identify a learning curve in hospitals with highest inclusion rates, an issue that was not addressed by Begg et al. We found a higher composite score for hospitals with a low accrual rate compared to hospitals with a high accrual rate. Although some studies showed lower performance scores for hospitals with low accrual rates(42), results of other studies did not show any correlation between accrual rates and clinical trial performance.(47, 49) This latter observation implicates that hospitals with low accrual rates, which are often regional hospitals, should not be excluded and may be even encouraged to participate in clinical trials.(48)

In our study, we evaluated and compared trial performance between (different categories of) hospitals with a newly introduced composite score, because no scoring system for trial performance exists. However, the usability and validity of this score needs to be determined in follow-up studies. We were not able to explain the variation in our composite score between hospitals, even though we included data from three large clinical trials. This implies that, without proper validation, our composite score should be used with caution for comparison between hospitals. However, a possible implication for our composite score could be evaluation of trial performance per individual centre over time. This is supported by our finding of a learning curve for individual hospitals with a

high inclusion rate. An explanation for the learning curve could be an improved comprehension of and experience with the study protocol after inclusion of several patients. An important implication is to optimize support of participating hospitals during trials to prevent protocol deviations, with specific focus on the first patients included.
Clinical trials are essential for improvement of treatment possibilities. High quality within these trials is a requisite for reliable evidence-based outcomes. There is a current need for an evidence-based instrument to evaluate trial performance between hospitals, possibly with an adjusted version of our composite score included. Evaluation and validation should be performed in different studies and research areas, to make it more widely applicable.

In conclusion, trial performance, evaluated with a composite score including stratification errors, major protocol violations, SAE reporting and the inclusion of ineligible patients, was comparable between different types of hospitals. In the highest including hospitals we identified a learning curve for trial performance. Consequently, we recommend additional support during the first patient inclusions in every participating centre, to prevent stratification errors, ineligibility and major protocol violations. For individually-based hospital evaluation, our composite score could be used as a quality metric for trial performance.

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Chapter 6

Summary and discussion

Prospective monitoring of fatal serious adverse events

Early and correct assessment of treatment-related mortality is highly important in cancer clinical trials. For a real-time knowledge of this crucial information, Serious Adverse Events (SAE) have to be reported within 24 hours. The SAE reports are collected centrally, assessed by the principal investigator(s) (PI) and/or study coordinators, and finally submitted to an independent data monitoring committee (IDMC). This system of early safety monitoring of clinical trials by the PI and IDMC largely depends on the early and reliable assessment of SAE reports. In **Chapter 2** we assessed the quality of Serious Adverse Event (SAE) reporting. The study coordinators performed on site monitoring of the individual charts of all patients who died within 30 days of the last administration of study drugs, except if death was clearly caused by disease progression. All these deaths had been reported as SAE. The relationship between treatment and death was categorized as unrelated, remote, possible, or probable, and submitted to the IDMC of the study. Forty out of 112 patients who died within 30 days qualified for review. The relationship between cause of death and study drugs as initially reported by the local investigator was changed in 26 patients (65%). In 12 out of 14 patients with a probable relationship between cause of death and study treatment a major protocol violation (MPV) was identified. In addition to the MPVs, four patients were considered ineligible for study participation which was not detected after standard data processing. We concluded that there was little agreement between the local investigator and the IDMC concerning the relationship between death within 30 days of last study treatment and treatment itself, and that study treatment as a cause of death is frequently underestimated. This quality control showed that the assessment of SAEs can improve the quality of safety results.

Discussion

This process of on site monitoring of fatal serious adverse events by the study coordinators revealed relevant and new information, such as MPVs and patient ineligibilities, which was not detected by routine data management. Patients were included who did not fulfil the safety criteria for the study drugs, and/or dose adjustments were not performed when indicated as stated by the protocol. Severe toxicity occurred in these patients subsequently leading to death. These incidents underscore the importance of educating medical staff and patients. Feedback was provided to the local investigators, in order to improve local procedures and prevent unnecessary toxicity and treatment related deaths in the future. We recommend on site monitoring by experts for

fatal serious adverse events which are not clearly related to disease progression in addition to regular on site monitoring in oncology clinical trials.

Comparison of treatment outcome in a clinical trial versus daily practice

Although not supported by solid evidence, it is generally thought that treatment of patients within the scope of a clinical trial may improve their outcome, for instance due to the fact that these patients receive more attention compared to patients who are treated outside clinical trials. In the CAIRO study, cytotoxic drugs were used at doses and schedules standard in daily practice, as were the eligibility and safety criteria. This allowed a comparison between trial patients and patients treated outside the trial.
To achieve a timely completion of trials it is important to include as many patients as possible in a clinical trial. A commonly reported participation rate is 5-14 % in all cancer patients and 30 % in more selected populations. National data of the Netherlands Cancer Registry (NCR) made it possible to estimate the participation of colorectal cancer patients in trials during the inclusion period of the CAIRO trial. In **Chapter 3** we compare the treatment outcome of patients with metastatic colorectal cancer included in this trial versus that of patients treated in daily practice. Stage IV colorectal cancer patients treated in the CAIRO trial were compared to patients treated the same way outside this trial in a representative selection of 29 Dutch hospitals during the trial accrual period in. Non- trial patients were identified by the NCR, and were checked for eligibility criteria of the CAIRO study. During the inclusion period 1946 stage IV colorectal cancer patients were registered in the NCR who received chemotherapy, of whom 394 patients were included in the CAIRO trial (20 %). We observed no difference in median overall survival between patients included in the clinical trial and eligible patients treated during the same period outside the trial in daily practice (HR 1.03, p=0.70). However, patients treated outside the trial who did not fulfil the standard eligibility criteria, but did receive comparable chemotherapy schedules had a significantly worse outcome (HR 1.7, $p < 0.01$). We conclude that trial results can only be extrapolated to the general population if the same patient selection criteria are applied. We observed that 20 % of all patients with stage IV colorectal cancer receiving chemotherapy, participated in the CAIRO trial. When all diagnosed stage IV patients were considered the overall trial participation was 10 %.

Discussion

The external validity of trial results is a continuing matter of concern. We observed no difference in outcome between patients participating in a trial and those who were treated in daily practice during the same period with the same drugs and regimens and who met the trial eligibility criteria. This strongly supports the external validity of this trial. However, a significantly worse

outcome was observed in non-trial patients who were treated with the same chemotherapy but who did not meet these eligibility criteria. Our findings strongly caution against the use of cancer drugs in daily practice in patients who do not meet the eligibility criteria of the trial(s) in which the efficacy of these drugs was demonstrated. If these patients are being treated after all, careful monitoring of results is warranted. Validation of trial results for daily practice remains a matter of high priority. The currently ongoing observational cohort study in The Netherlands, the Prospective Dutch Colorectal Cancer Cohort (PLCRC), is a useful instrument to prospectively investigate treatment outcome in daily practice. This study will make it possible to assess the use of different therapies in daily practice and to compare the outcome to trial patients. It will also be a way to prospectively follow patients who do not fulfil the safety criteria and do receive a certain drug regimen.
Our analysis also allowed the assessment of trial participation. The CAIRO trial had a high participation rate of 20% which exceeds the commonly reported 5-14% participation rate in cancer trials. The simple and straightforward design of the trial, its use of standard drugs and the clinically relevant study objective will likely have had a positive effect on trial participation.

Prognostic value of WHO performance status and QoL in colorectal cancer patients

Performance status (PS) is an established prognostic factor in patients with advanced cancer, and is usually scored by the treating physician. The EORTC QLQ-C30 questionnaire as reported by cancer patients is a validated tool to assess quality of life. Subjectivity plays a role in both assessments, and data on a direct comparison are scarce. In **Chapter 4** the prognostic value of the WHO performance status was compared with the physical functioning (PF) scale of the QLQ-C30 in a prospective randomised phase 3 trial in advanced colorectal cancer, the CAIRO study. Patients were divided into 2 groups based on the baseline physical functioning(PF) scales of the EORTC QLQ-C30. QoL was considered "good" if the PF score was higher than 66.7%. "Poor" QoL was defined as a PF scored 66.7% or less. The prognostic value in terms of median overall survival of both assessments was compared. Results were validated in the CAIRO2 study. The median OS for patients with a "good" QLQ-C30 PF and a "poor" PF in patients with WHO PS 0, was 20.3 months (n=300) and 10.4 months (n=44), in patients with WHO PS 1 16.8 months (n=125) and 10.1 months (n=63), and in patients with WHO PS 2 16.2 months (n=11) and 9.9 months (n=12), respectively. In a Cox regression model which included other prognostic factors, "good" versus "poor" QLQ-C30 PF was significantly prognostic for overall survival (0.57 95% CI 0.46-0.72), but not WHO PS. These results were confirmed in the CAIRO2 study. We concluded that patient reported QLQ-C30 PF was more prognostic than the physician reported WHO PS.

Discussion

The CAIRO study investigated the optimal use of standard chemotherapy regimens in patients with advanced colorectal cancer. During the analysis of the data from this study, we sometimes observed a discrepancy between the WHO PS as scored by physicians and the 5 physical functioning items from the EORTC QLQ-C30 as scored by patients at baseline. For example, a patient with an investigator assigned WHO PS score of 0 reported that he had quite a bit trouble taking a short walk.

Therefore we performed an overall comparison of physician- versus patient-reported physical performance in relation to the median OS. Within each group of the WHO PS we observed a large difference in QLQ-C30 PF. Patients with a WHO 1 and good QLQ-C30 PF had a better median overall survival than patients with WHO 0 and a poor QLQ-C30 PF. Other items of the QLQ-C30 such as social functioning have previously shown a prognostic value for OS. We used the 5 physical functioning items of the QLQ-C30, because these items most optimally reflect the general health status of a patient. WHO PS is an established

prognostic factor and is often used as a stratification factor and an inclusion criterion. It has been observed in other studies that physicians are more likely to assign a better score to patients than patients do to themselves. We have validated these subjective measures by the objective outcome measure OS, and found the patient reported QLQ-C30 PF to be more prognostic than WHO PS as scored by physicians. We therefore recommend to include patient reported outcomes instead of physician-reported performance status as a stratification factor in clinical (cancer) trials. Obviously this should be done with an internationally accepted questionnaire, and the EORTC QLQ-C30 with translations and validations in 90 different languages appears to be a good option.

Clinical trial performance in metastatic colorectal cancer

The quality of data that are derived from clinical trials is dependent of many factors. These include the requirement for adequate methodology and protocols in order to maintain reliability and validity of the obtained results. Although no validated indicators for clinical trial performance are available, a potentially useful criterion for clinical trial adherence may be the number of protocol violations. However, data on the level of protocol adherence are scarce. Major protocol violations are defined as deviations, which may result in harm to the patient and which may impact the integrity of data. The number of study participants included per participating hospital in multicenter trials has been suggested as a potential indicator of trial performance. Conflicting results regarding the influence of hospital type on trial performance have been reported. In **Chapter 5** we report the evaluation of clinical trial performance with a composite score in three large phase 3 clinical trials with systemic treatment in colorectal cancer in The Netherlands. This score included stratification errors, major protocol violations, SAE reporting and the inclusion of ineligible patients. These data were supplemented with a hospital survey containing questions about the number of beds, medical oncologists and research nurses. Hospitals were divided into 3 categories: university-, teaching-, and regional hospitals. Inclusion rates were higher in university hospitals and teaching hospitals compared to regional hospitals. A large variation in trial performance was observed between hospitals, but individual factors (number of beds, number of medical oncologists, presence of research nurse) could not be identified which could explain this variation. No difference in trial performance was found between the three hospital categories. Hospitals with a low accrual rate had a higher performance score compared to hospitals with a high accrual rate. We observed a learning curve in hospitals with high accrual rates, as more errors/violations were observed in the first three included patients per trial.

Discussion

Trial performance, evaluated by a composite score including stratification errors, major protocol violations, SAE reporting and the inclusion of ineligible patients, was comparable between different types of hospitals. We were not able to explain the variation in our composite score between hospitals, even though we included data from three large clinical trials. This implies that, without proper validation, our composite score apparently is insufficient as an instrument to evaluate the trial performance of hospitals. However, our finding of a learning curve in individual hospitals with a high inclusion rate may suggest a possible use for our composite score to evaluate trial performance per

individual centre over time. Apparently, the experience with the study protocol in practice (i.e. after inclusion of several patients) has a relevant impact on the quality of trial performance. This may imply either a more intensive training schedule before initiation of a trial, and/or increased support during the treatment per protocol of the first included patients.

Nederlandse samenvatting

Samenvatting

Dikke- darm en endeldarm kanker (colorectaal carcinoom, CRC) is een van de meest voorkomende vormen van kanker in de westerse wereld. Ongeveer 50 % van de patiënten ontwikkelt in de loop van de ziekte uitzaaiingen. De meerderheid van deze patiënten zullen behandeld worden met palliatieve systemische therapie. De laatste decennia zijn de opties voor systemische behandeling aanzienlijk verbeterd, van 5-FU als de enige beschikbare chemotherapie naar de behandeling met andere cytotoxische middelen zoals oxaliplatin en irinotecan, en doelgerichte behandelingen zoals antilichamen tegen de vasculaire endotheliale groeifactor (VEGF) en de epidermale groeifactor receptor (EGFR). Deze nieuwe therapieën en de toename van het aantal chirurgische resecties van metastasen hebben geleid tot een stijging van de mediane overleving van 10-11 maanden tot op het ogenblik ongeveer 30 maanden.

De Dutch Colorectal Cancer Group (DCCG) is een nationale multidisciplinaire studiegroep met als doel het stimuleren van klinisch onderzoek en het verbeteren van de kwaliteit van de diagnose en behandeling van patiënten met colorectaal carcinoom in Nederland. In januari 2003 is de DCCG de CAIRO studie gestart, een gerandomiseerde fase 3 studie in patiënten met gemetastaseerd colorectaal carcinoom (mCRC). Daarna zijn er 2133 patiënten met mCRC behandeld in drie opeenvolgende fase 3 studies. De vierde, vijfde en zesde zijn op dit moment open voor inclusie. CAIRO is een acroniem voor de geneesmiddelen gebruikt in de eerste studie: Capecitabine, IRinotecan en Oxaliplatin. De resultaten van deze 3 studies zijn geïmplementeerd in de nationale en internationale richtlijnen.

Prospectief monitoren van dodelijke ernstige ongewenste voorvallen

Vroege en correcte beoordeling van overlijdens gerelateerd aan de behandeling is belangrijk in oncologisch onderzoek. Om zonder vertraging deze cruciale informatie te verzamelen moeten ernstige ongewenste voorvallen (SAE's) binnen 24 uur gemeld worden. De SAE's worden centraal verzameld, beoordeeld door de hoofdonderzoeker(s) en/of studiecoördinator. Daarna worden de SAE's beoordeeld door een onafhankelijke commissie, de Independent Data Monitoring Committee (IDMC). Dit systeem om de veiligheid te monitoren is sterk afhankelijk van de vroege en betrouwbare beoordeling van SAE's. In **hoofdstuk 2** bekijken we de kwaliteit van het rapporteren van SAE's. De studiecoördinatoren hebben op locatie in het ziekenhuis de statussen van alle patiënten ingezien die binnen 30 dagen na de laatste toediening van de

chemotherapie overleden, behalve als er duidelijk sprake was van progressieve ziekte. Alle overlijdens binnen 30 dagen waren gemeld als SAE. De relatie van de behandeling met de studiemedicatie werd ingedeeld in niet, gering, mogelijk, waarschijnlijk en zeker gerelateerd, en werden daarna ingediend bij de IDMC van de studie. Veertig van de 112 patiënten die binnen 30 dagen waren overleden voldeden aan de criteria voor beoordeling. De relatie tussen de doodsoorzaak en de studiemedicatie zoals in eerste instantie gerapporteerd door de lokale onderzoeker werd veranderd in 26 patiënten (65 %). In 12 van de 14 patiënten met een waarschijnlijke relatie tussen de studiemedicatie en het overlijden werd een ernstige protocol afwijking (MPV) gevonden. Naast de MPV's werden ook vier patiënten gevonden die niet voldeden aan de in- en exclusiecriteria van de studie. Deze informatie was niet eerder gevonden tijdens reguliere verwerking van de gegevens. We concludeerden dat er weinig overeenkomst was tussen de lokale onderzoeker en de IDMC in de beoordeling van de relatie tussen de studiebehandeling en het overlijden binnen 30 dagen na de laatste studiebehandeling, en dat de studiebehandeling als doodsoorzaak vaak onderschat wordt. Deze kwaliteitscontrole verbetert de beoordeling van de veiligheid van de studiemedicatie.

Een vergelijking van de behandeluitkomsten in een klinische trial versus de dagelijkse praktijk

Al is het niet ondersteund door bewijs, er wordt over het algemeen gedacht dat de behandeling van patiënten binnen studieverband de uitkomst verbetert, bijvoorbeeld doordat deze patiënten meer aandacht krijgen in vergelijking met patiënten die buiten een studie behandeld worden. In de CAIRO studie werden cytostatica gebruikt in een standaard schema uit de dagelijkse praktijk op standaard doseringen, evenals de toelatings-voorwaarden en veiligheidscriteria. Dit maakte het mogelijk een vergelijking te maken tussen patiënten in een trial en patiënten uit de dagelijkse praktijk.
Om een tijdige voltooiing van studies mogelijk te maken is het belangrijk om zo veel mogelijk patiënten in trials te includeren. Een gebruikelijke behaalde participatie is 5-14% binnen alle kankerpatiënten en 30% in meer geselecteerde populaties. Met behulp van gegevens uit de Nederlandse Kankerregistratie (NKR) was het mogelijk om de deelname van darmkanker patiënten in studies tijdens de inclusie periode van de CAIRO studie te bepalen. In **hoofdstuk 3** vergelijken we de uitkomst van de behandeling van patiënten met gemetastaseerde darmkanker geïncludeerd in deze trial met patiënten die behandeld zijn in de dagelijkse praktijk. Stadium IV darmkanker patiënten behandeld in de CAIRO studie werden vergeleken met patiënten in de zelfde periode de zelfde behandeling kregen in de dagelijkse praktijk in 29

Nederlandse ziekenhuizen. Patiënten behandeld buiten studieverband werden uit de NKR gehaald en in de status gecheckt op de in- en exclusiecriteria van de CAIRO studie. Tijdens de inclusieperiode werden er 1946 stadium IV darmkanker patiënten geregistreerd in de NKR die een behandeling met chemotherapie kregen. Hiervan waren er 394 patiënten geïncludeerd in de CAIRO studie, 20 %. We zagen geen verschil in overleving tussen patiënten die deelnamen aan de studie en patiënten die in aanmerking hadden kunnen komen die in de dagelijkse praktijk behandeld werden (HR 1.03, p=0.70). Echter, patiënten die tijdens de zelfde periode werden behandeld buiten studieverband, die niet aan de in- en exclusiecriteria voldeden hadden een significant slechtere uitkomst (HR 1.7, p<0.01). We concluderen dat studie-resultaten alleen naar de algehele populatie geëxtrapoleerd kunnen worden als de zelfde selectiecriteria worden toegepast. We zagen dat 20 % van alle patiënten met stadium IV darmkanker die chemotherapie kregen, deelnamen aan de CAIRO studie. Als we alle gediagnostiseerde stadium IV patiënten meenemen is de deelname aan de studie 10 %.

De prognostisch waarde van de WHO performance status en kwaliteit van leven in darmkanker patiënten

De performance status (PS) is een bekende prognostisch factor in patiënten met kanker en wordt normaal gescoord door de behandeld arts. De EORTC QLQ-C30 vragenlijst ingevuld door patiënten is een gevalideerde methode om de kwaliteit van leven (KvL) te bepalen. Subjectiviteit speelt mee in beide methoden, en gegevens over een onderlinge vergelijking zijn er niet veel. In **hoofdstuk 4** hebben we binnen de CAIRO studie de prognostische waarde van de WHO PS vergeleken met de Physical function (PF) schaal van de QLQ-C30. Patiënten werden verdeeld in 2 groepen op basis van de uitgangswaarde van de Physical function schaal van de EORTC QLQ-C30. KvL werd beschouwd als "goed" als de PF score hoger was dan 66.7 %. "Slechte" KvL was gedefinieerd als aan PF score van 66.7 % of minder. De prognostische waarde van de WHO PS en de PF schaal op de overleving werden met elkaar vergeleken. Deze resultaten werden daarna gevalideerd in de CAIRO2 studie.
De mediane overleving voor patiënten met een 'goede" QLQ-C30 PF en een "slechte" PF in patiënten met WHO PS 0, was 20.3 maanden (n=300) en 10.4 maanden (n=44), in patiënten met WHO PS 1 16.8 maanden (n=125) en 10.1 maanden (n=63), en in patiënten met WHO PS 2 16.2 maanden (n=11) en 9.9 maanden (n=12). In een Cox regressie model waarbij andere prognostische factoren werden toegevoegd was "goede" versus "slechte"QLQ-C30 PF een significante prognostische factor voor overleving (HR 0.57 95% CI 0.46-0.72), WHO PS niet. Deze resultaten werden bevestigd in de CAIRO2 studie. We

concludeerden dat door patiënten gerapporteerde QLQ-C30 PF beter voorspellend was dan de door de arts gerapporteerde WHO PS.

De kwaliteit van klinische trials in gemetastaseerde darmkanker

De kwaliteit van gegevens uit klinisch onderzoek is afhankelijk van veel verschillende factoren. Onder andere het gebruik van adequate methodologie en protocollen om betrouwbare en valide resultaten te verkrijgen. Ondanks dat er geen valide indicatoren voor de uitvoer van klinisch onderzoek zijn, zou het aantal afwijkingen van het studieprotocol mogelijk een toepasbare indicator zijn voor de naleving van het protocol. Gegevens over de naleving van studie protocollen zijn echter schaars. Ernstige afwijkingen van het protocol zijn gedefinieerd als afwijkingen die zouden kunnen leiden tot schade bij de patiënt of die een impact zouden kunnen hebben op de integriteit van de gegevens. Het aantal geïncludeerde studie patiënten per deelnemend ziekenhuis is eerder voorgesteld als een mogelijke indicator voor de kwaliteit van klinisch onderzoek. Er zijn tegenstrijdige resultaten over de invloed van het type ziekenhuis op de kwaliteit van klinisch onderzoek. In **hoofdstuk 5** rapporteren we de evaluatie van de kwaliteit van klinisch onderzoek door middel van een samengestelde score in drie grote fase 3 studies met systemische behandeling in darmkanker patiënten in Nederland. Deze score bestond uit stratificatiefouten, ernstige afwijkingen van het protocol, SAE rapportage en de inclusie van patiënten die niet aan de in- en exclusiecriteria voldeden. Hiernaast hebben we een vragenlijst verstuurd naar de ziekenhuizen waarin onder andere werd gevraagd naar het aantal bedden, medisch oncologen en researchverpleegkundigen. Ziekenhuizen werden verdeeld in 3 categorieën: universitaire, opleidings- en regionale ziekenhuizen. De inclusie was hoger in de universitaire en opleidings- ziekenhuizen vergeleken met de regionale ziekenhuizen. Een grote variatie werd gezien in de uitvoer van een studie tussen ziekenhuizen, maar individuele factoren zoals het aantal bedden, het aantal medisch oncologen of de aanwezigheid van een researchverpleegkundige konden deze variatie niet verklaren. Er werd geen verschil in de kwaliteit van klinisch onderzoek gezien tussen de drie typen ziekenhuizen. Ziekenhuizen met een lage inclusie hadden een hogere score vergeleken met ziekenhuizen met een hoge inclusie. We zagen een leercurve in ziekenhuizen met een hoge inclusie, in de eerste drie geïncludeerde patiënten werden meer fouten gezien dan daarna.

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Dankwoord

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Curriculum vitae

Curriculum vitae

Linda Mol is op 8 augustus 1979 in Vlissingen geboren. In 1997 behaalde zij haar VWO diploma aan de Stedelijke scholengemeenschap De Rede in Terneuzen. Van 1997 tot 2002 studeerde zij Biomedische Gezondheids-wetenschappen aan de Katholieke Universiteit Nijmegen, thans Radboud Universiteit, met als afstudeerrichting Bewegingswetenschappen.

Na het behalen van haar doctoraal Biomedische Gezondheidswetenschappen in 2002 begon zij als datamanager bij het Integraal Kankercentrum Oost (IKO) te Nijmegen alwaar zij in 2005 de overstap maakte als centraal datamanager van de CAIRO studie. In 2007 begon zij dit werk te combineren met dit onderzoek. Het IKO is gefuseerd tot IKNL, waar Linda werkzaam is als centraal datamanager. Van 2010 tot 2016 was zij lid van de commissie klinische studies van KWF Kankerbestrijding.

Linda Mol is getrouwd met Maurice de Jongh en samen hebben ze twee kinderen, Anouk (2011) en Jasper (2014).