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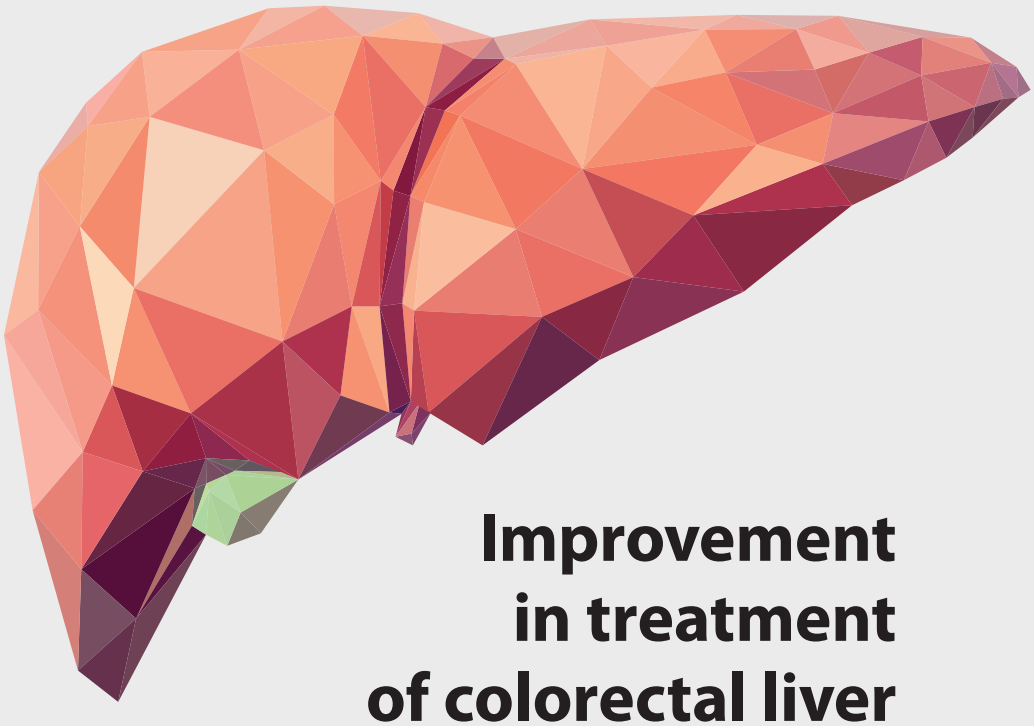

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Joost Huiskens

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Voor Johanna

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Improvement in treatment of colorectal liver metastases and the conduct of clinical research

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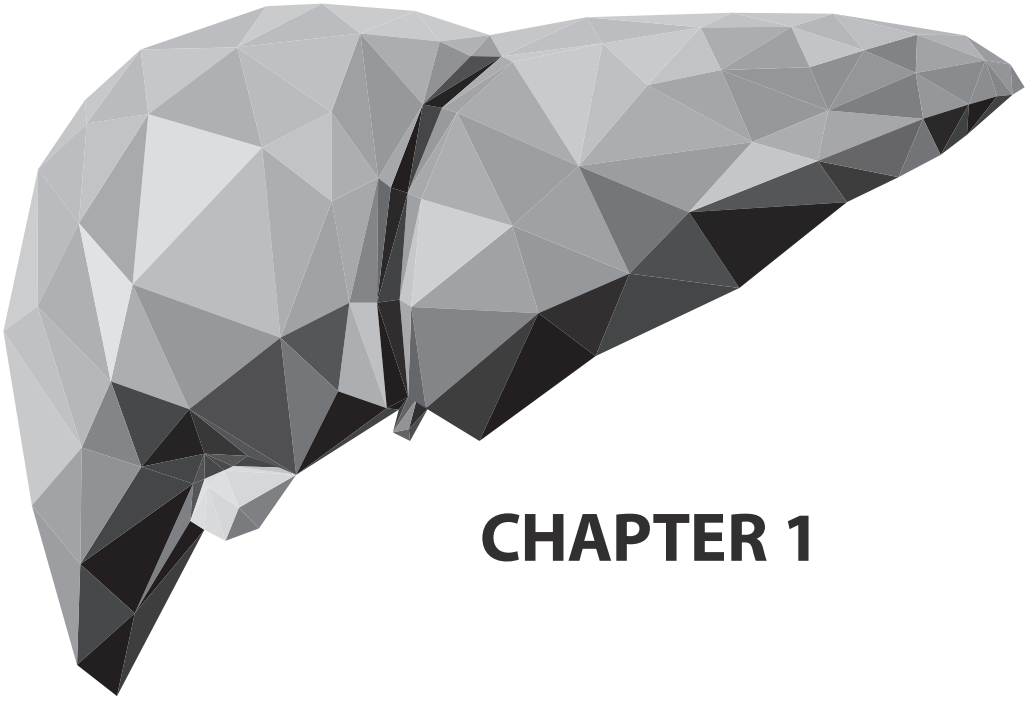

CHAPTER 1

General Introduction and Outline of the Thesis

PART 1

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide.[1] Most cancer deaths are the result of progression of metastases.

Survival rates in patients with metastatic CRC have increased over the past decades owing to the increased resection rate of metastases and the development of effective systemic drugs. In 30-40% of patients, CRC metastases are limited to the liver.[2,3] Resection of colorectal liver metastases (CRLM) offers the chance of long-term disease-free survival or cure, with 5-year survival rates of resection ranging between 25% and 58%.[4–6]

In addition to standard, one-stage resections, several other options are currently available to achieve clearance of the liver from all tumors. The combination of resection with local ablative techniques enables sparing of parenchyma. Preoperative portal vein embolization can be used to induce hypertrophy of the future liver remnant rendering patients with upfront too small liver remnant amenable to resection.[7] Two-stage hepatectomy and Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) are strategies to allow extensive resections in patients with bilobar metastases. Despite these novel techniques, only the minority of patients with CRLM (20%) present with metastases deemed resectable upfront.[8,9]

In patients with upfront unresectable CRLM, a number of studies have shown that downsizing of CRLM by induction systemic treatment may allow secondary resections with survival rates similar to primary resections.[10–12] However, there is no consensus regarding the optimal systemic therapy regime. The effect of systemic treatment varies between patients, some have total response and others show progression of disease.[10]

Chapter 1 describes the protocol of the multicenter, randomized, phase 3 clinical trial CAIRO5. CAIRO5 is a prospective multicenter trial that investigates the optimal systemic induction therapy for patients with initially unresectable, liver-only colorectal cancer metastases. Decision making on optimal treatment strategy in patients with initially unresectable colorectal cancer liver metastases (CRLM) remains complex because uniform criteria for (un)resectability are lacking. In **Chapter 2** we evaluated the feasibility and short-term outcomes of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel. This study analyzed prospective resectability evaluation of patients with CRLM by a panel of radiologists and liver surgeons.

The improvement of surgical techniques has increased the resection rates of patients with CRLM. Preoperative portal vein embolization (PVE) is a technique in which one side of the portal venous system is occluded to induce hypertrophy of the contralateral liver lobe. PVE is currently considered the golden standard to preoperatively increase the FLR when it's volume is less than 20-30% in order to decrease the risk of liver failure.[13,14] There is an ongoing controversy surrounding PVE regarding the short-term safety of PVE and long-term

oncological benefit. **Chapter 3** aims to compare survival outcomes of patients subjected to major liver resection for colorectal liver metastases (CRLM) with or without PVE.

Another new method to induce liver regeneration is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS).[15] This new type of two-stage hepatectomy induces extensive and rapid liver regeneration. ALPPS allows the resection of colorectal liver metastases (CRLM) with curative intent which would otherwise be unresectable and only eligible for palliative systemic therapy. The oncological outcomes of CRLM patients following ALPPS are uncertain.[16–19] **Chapter 4** compares the outcomes of ALPPS in patients with otherwise unresectable CRLM with matched historic controls treated with palliative systemic treatment. **Chapter 5** aims to establish a risk-score to avoid adverse outcomes of ALPPS only for patients with CRLM as primary indication for ALPPS.

Hepatic vascular inflow occlusion (VIO) can be applied during resection of CRLM to control intra-operative blood loss but has been linked to accelerated growth of micro metastases in experimental models.[20–22] In **Chapter 6** we investigated the effects of hepatic VIO on disease-free and overall survival in patients following resection for CRLM.

PART 2

Prospective randomised trials such as the CAIRO5 trial are considered the best instrument to test the effectiveness of medical interventions and are therefore at the core of 'evidence-based' healthcare. This research typically involves a large number of patients, and therefore the participation of multiple centres. The initiation and conduct of these multicentre studies require a significant investment of time and money. The Netherlands have an excellent track record of investigator-initiated clinical research which is considered due to a well organised research infrastructure in which academic and general hospitals are actively participating.[23] Central medical ethical approval and subsequent local approval of the participating centres for feasibility are required before a trial can be initiated. The increasing complexity and diversity of the procedure to obtain approval for local feasibility causes delay and increases costs.[24–29] This hampers the conduct of clinical research in The Netherlands. In **Chapter 7**, the procedures for obtaining approval for local feasibility of two national investigator-initiated, multicentre phase 3 studies in colorectal cancer were evaluated.

Patients who give informed consent to participate in scientific research and thereby agree to exposure to an experimental treatment do so under the assumption that they contribute to medical science. If investigators fail to publicly communicate these results this contribution is nullified and the conditions for the initial agreement for participation are not met. Moreover, the validity of clinical trial results starts with a carefully designed and conducted trial. Adherence to the trial protocol in the eventual trial report is essential in minimising bias and prevention of selective reporting. Since July 2005, the International

Committee of Medical Journal Editors (ICMJE) requires trials to be registered before the enrolment of the first patient in order to prevent selective publication of trial outcomes in an effort to reduce this form of publication bias.[30] In **Chapter 8** the results of a study in which publication rates, timely dissemination of results and the prevalence of consistency in hypothesis, sample size and primary endpoint of Dutch investigator-initiated randomized controlled clinical trials are presented.

The number of registered clinical trial protocols on clinicaltrials.gov has increased from 12,020 in 2005, to over 230,000 in 2017 and the yearly number of newly registered studies is approaching 30,000.[31] In the field of colorectal cancer alone, the third most common cancer worldwide, 4,482 trials were registered by the end of 2017.[32] Besides the increasing number of clinical trials, there has been an increase in protocol design complexity during the past decade. Among many others, these factors lead to shortage of both knowledge and time for healthcare professionals to participate in clinical trials.[33,34] The complexity of clinical trials can hamper the inclusion of patients, which is the leading cause of problems in the conduction of clinical trials.[35–38] **Chapter 9** illustrates the design of a smartphone application that provides easy to access and up to date information on ongoing Dutch clinical trials for patients with colorectal cancer. The chapter also presents the results of the usability and satisfaction of the application two years after its introduction.

A randomized controlled trial of poor methodological quality may produce unreliable results with potentially harmful consequences when implemented in a clinical setting.[39] In order to use the information coming from trials, it is essential to assess the potential risk of bias and the certainty of the results. Therefore, this is considered as one of the evidence-based medicine core competencies for healthcare professionals. However, it requires skills and time to extensively read an article.[40]

As medical information gets increasingly more accessible, laymen (e.g. science journalists, family members of patients) with limited scientific experience should be able to assess the methodological quality of studies when interpreting their results. It might be so that current methodological assessment tools are ill suited for a less experienced public. As a consequence, laymen might attribute an incorrect value to scientific results. In **Chapter 10** the results of the consistency of risk of bias assessment between individuals with limited scientific experience and experienced Cochrane review author teams are presented.

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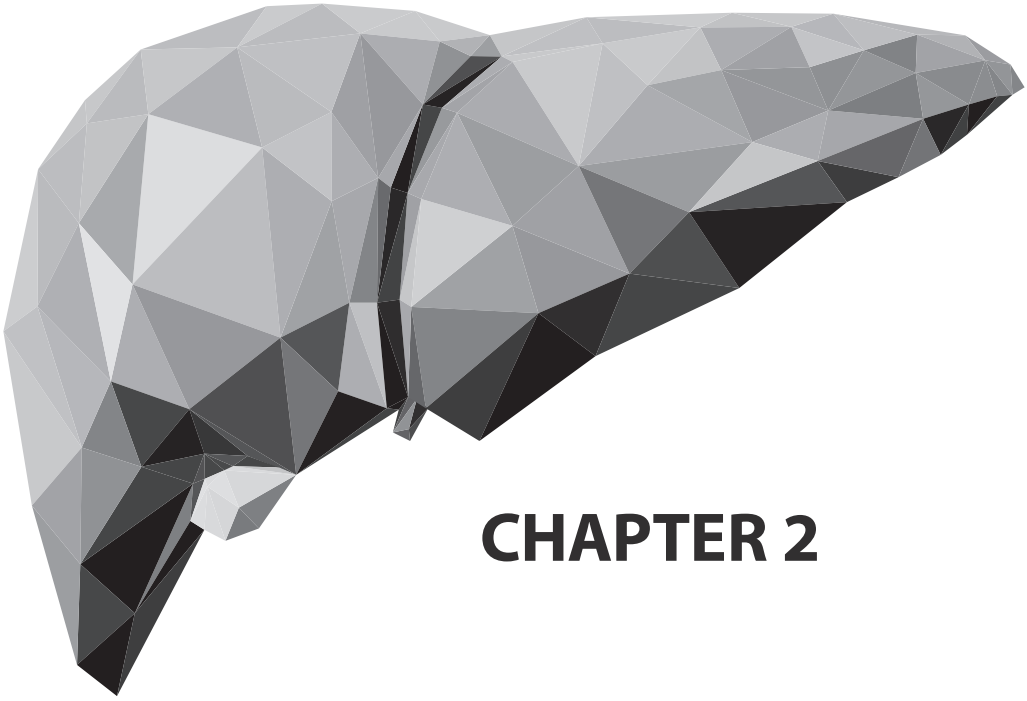
PART I



CHAPTER 2

Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, a study protocol of the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG)

Joost Huiskens, Thomas M van Gulik, Krijn P van Lienden, Marc RW Engelbrecht, Gerrit A Meijer, Nicole CT van Grieken, Jonne Schriek, Astrid Keijser, Linda Mol, I Quintus Molenaar, Cornelis Verhoef, Koert P de Jong, Kees HC Dejong, Geert Kazemier, Theo M Ruers, Johanus HW de Wilt, Harm van Tinteren, Cornelis JA Punt

BMC Cancer. 2015

ABSTRACT

Background

Colorectal cancer patients with unresectable liver-only metastases may be cured after downsizing of metastases by neoadjuvant systemic therapy. However, the optimal neoadjuvant induction regimen has not been defined, and the lack of consensus on criteria for (un)resectability complicates the interpretation of published results.

Methods/design

CAIRO5 is a multicentre, randomised, phase 3 clinical study. Colorectal cancer patients with initially unresectable liver-only metastases are eligible, and will not be selected for potential resectability. The (un)resectability status is prospectively assessed by a central panel consisting of at least one radiologist and three liver surgeons, according to predefined criteria. Tumours of included patients will be tested for *RAS* mutation status. Patients with *RAS* wild type tumours will be treated with doublet chemotherapy (FOLFOX or FOLFIRI) and randomised between the addition of either bevacizumab or panitumumab, and patients with *RAS* mutant tumours will be randomised between doublet chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab or triple chemotherapy (FOLFOXIRI) plus bevacizumab. Radiological evaluation to assess conversion to resectability will be performed by the central panel, at an interval of two months.

The primary study endpoint is median progression-free survival. Secondary endpoints are the R0/1 resection rate, median overall survival, response rate, toxicity, pathological response of resected lesions, postoperative morbidity, and correlation of baseline and follow-up evaluation with respect to outcomes by the central panel.

Discussion

CAIRO5 is a prospective multicentre trial that investigates the optimal systemic induction therapy for patients with initially unresectable, liver-only colorectal cancer metastases.

Trial registration

CAIRO 5 is registered at European Clinical Trials Database (EudraCT) (2013-005435-24).
CAIRO 5 is registered at ClinicalTrials.gov: NCT02162563, June 10, 2014.

Keywords

Unresectable colorectal liver metastases, Treatment strategies

BACKGROUND

Approximately 50% of patients with colorectal cancer (CRC) will develop metastases, either at presentation or during follow-up. Colorectal cancer disseminates predominantly to the liver [1]. The 5-year overall survival rates in patients with metastatic CRC have increased over the past decades due to the availability of more effective drugs and the increased use of resection of metastases, and is currently around 20% [2]. Complete resection of metastases offers the only chance for cure, however a minority of patients (approx. 20%) present with resectable metastases. Evidence for the benefit of neoadjuvant chemotherapy with the objective to improve resectability rates was already established in 1996, at which time it was shown that initially unresectable metastases could become resectable (further defined as secondary surgery) after downsizing by chemotherapy [3]. Currently there is consensus that combination chemotherapy should be part of this neoadjuvant regimen, however there is no consensus regarding the selection of targeted therapy.

Secondary liver resections after neoadjuvant systemic treatment

Data from a single institution by Adam et al. [4] have shown that of 1104 patients with metastases confined to the liver, 12.5% of patients became eligible for secondary surgery, and that these patients had a 5-year survival rate of 33%. The benefit of primary or secondary surgery has not been evaluated in prospective randomised studies. However, given the consistent data from published series, there is little doubt that a complete resection (primary or secondary) of liver metastases prolongs survival. Indeed, in the liver survey database the survival benefits of secondary surgery are close to those of primary surgery, and better than for systemic therapy alone [5].

A major problem in interpretation of the results of these studies is the lack of consensus on the criteria for resectability, as has been shown in the CELIM study [6]. This complicates the interpretation of the results from studies involving patients with unresectable liver-only metastases, and even more of the results on secondary resection rates as reported from retrospective subgroup analyses from phase 3 studies in unselected metastatic colorectal cancer patients.

Choice of chemotherapy regimen in neoadjuvant treatment

Randomised phase 3 studies have clearly shown that combination chemotherapy with a fluoropyrimidine plus irinotecan or oxaliplatin produces higher response rates compared with fluoropyrimidine monotherapy [7]. Therefore combination chemotherapy should be used when downsizing of metastases is the primary objective.

Studies on triple chemotherapy (5FU + oxaliplatin + irinotecan, FOLFOXIRI) have shown high response rates in phase-2 studies, but conflicting results on its survival benefit in two phase-3 studies [8-10]. However, retrospective analysis of both phase 3 studies showed that

the rate of secondary resections was increased, from 5 (12%) to 14 (36%) and from 6 (4%) to 14 (10%), respectively. It should be noted that secondary resections were not a prospective objective of these studies.

Neoadjuvant treatment with chemotherapy plus either anti-EGFR antibodies or bevacizumab

Given the slightly higher response rates of chemotherapy plus anti- EGFR antibodies (cetuximab, panitumumab) compared to chemotherapy plus bevacizumab in the first-line treatment of metastatic CRC patients, the use of cetuximab or panitumumab has been advocated in patients with potentially resectable liver metastases. However, an increase in the response rate has also been shown in some (but not all) phase 3 studies by the addition of bevacizumab to chemotherapy. Also high secondary R0 resection rates were obtained in phase 2 studies with chemotherapy plus bevacizumab [11,12]. Data from 2 randomised trials of a head-to-head comparison between bevacizumab and anti-EGFR therapy, both in combination with chemotherapy, do not show a significant difference in response rate and progression-free survival [13,14]. Also preliminary results of the larger CALGB 80405 trial do not show a significant difference in overall survival [15]. The results of the TRIBE study [16] showed a significant benefit in response rate for FOLFOXIRI + bevacizumab versus FOLFIRI + bevacizumab (65% versus 53%, respectively). However, this did not translate into an increased rate of secondary resections (15% versus 12%, and in patients with liver-only metastases 32% versus 28%, respectively).

Furthermore, the use of RECIST criteria in the evaluation of the effect of targeted therapies has been questioned, and data are accumulating that morphological criteria rather than RECIST criteria should be used to assess the efficacy of bevacizumab treatment [17,18].

As a backbone for the use of targeted therapies, currently no preferred chemotherapy regimen prevails. The benefit of bevacizumab and anti-EGFR antibodies has been shown in combination with both irinotecan- and oxaliplatin-containing regimens [19]. A head-to-head comparison of irinotecan- and oxaliplatin-containing regimens in combination with cetuximab has shown comparable results in patients with unresectable liver-only metastases [6]. However, the use of capecitabine in combination with anti-EGFR therapy is being discouraged [20].

Selection of patients for anti-EGFR therapy

Since the initial observation that *KRAS* mutation (exon 2, 3 en 4) is a negative predictive factor for anti-EGFR therapy [21], much effort has been made to further optimize patient selection for this therapy. Recently, the negative predictive value of *RAS* (*KRAS exon* 2,3 en4 and *NRAS* exon 2 and 3) mutations were confirmed [22,23]. *BRAF* mutation was shown to be prognostic, but not predictive [24,25].

METHODS/DESIGN

The objective of the CAIRO5 study is to provide prospectively derived data on neoadjuvant systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases while using uniform and transparent criteria for unresectability. Given the lack of a predictive model that allows the selection of patients in whom a secondary resection may be achieved, the inclusion is not limited to patients with potentially resectable metastases and we plan to include all patients with unresectable, liver-only metastases.

Patients with *RAS* wild type tumours are randomised between bevacizumab and panitumumab in combination with a two-drug combination chemotherapy (5-fluorouracil plus either irinotecan, FOLFIRI, or oxaliplatin, FOLFOX, according to choice of the local investigator). Although panitumumab and cetuximab were shown equally effective in patients with *KRAS* wild type tumours [26], we selected panitumumab as anti-EGFR antibody given the more mature data for panitumumb in relation to *RAS* mutation status. Patients with *RAS* mutated tumours will be randomised between FOLFOX/FOLFIRI (choice of investigator) plus bevacizumab and triple chemotherapy (FOLFOXIRI) plus bevacizumab. An innovative aspect of CAIRO5 is the prospective assessment of unresectability status and evaluation of treatment by a central panel of radiologists and liver surgeons, according to predefined and transparant criteria.

Objectives and hypotheses

The primary objective of this study in CRC patients with initially unresectable liver-only metastases is to compare the median progression-free survival (PFS) between the two treatment strategies in each of the two patient cohorts (*RAS* wild type and *RAS* mutant tumors, respectively). In patients with *RAS* wild type tumours it is hypothesized that FOLFOX or FOLFIRI + panitumumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab. In patients with *RAS* mutant tumours it is hypothesized that FOLFOXIRI + bevacizumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab.

Secondary objectives are to assess the secondary R0/1 resection rate, median overall survival, response rate, toxicity, pathological response in resected lesions, postoperative morbidity, and correlation of baseline and follow-up evaluation by the panel with outcome. Translational research will be performed on predictive and prognostic biomarkers and imaging methods.

Study design

The study is designed as a randomised phase 3 trial. For each candidate patient, a panel of at least 3 liver surgeons and one radiologist will evaluate the baseline CT scan of abdomen and liver for resectability or unresectability of liver metastases (see Panel procedure and evaluation).

Potentially eligible patients will be registered after informed consent has been obtained. Once eligibility has been confirmed, including the unresectabilty status of liver metastases as defined by the central panel, patients will be randomised and *KRAS (exon 2, 3 and 4), NRAS (exon 2 and 3) and BRAF* mutation status will be assessed using TSACP MiSeq analysis [27]. Patients with *RAS* wild type tumours are being randomised between doublet chemotherapy plus either bevacizumab or panitumumab. Patients with *RAS* mutated tumours are being randomised between doublet chemotherapy plus bevacizumab or triple chemotherapy plus bevacizumab. RAS wild type patients and RAS mutant patients will be randomised independently in a 1:1 ratio. Randomisation will be done using ALEA software (ALEA ®, FormsVision, Abcoude, the Netherlands).

Patients will be stratified for potential resectability of liver metastases (yes versus no, according to the central panel), serum LDH (normal versus abnormal), and treatment centre. Patients with *RAS* wild type tumours will also be stratified for *BRAF* mutation status (wild type versus mutated) and use of irinotecan- versus oxaliplatin-containing regimen. The flowchart of the study is shown in Figure 1.

Study population

Patients who meet the following inclusion criteria are eligible for participation in this trial: histological proof of colorectal cancer, previously untreated and unresectable metastases confined to the liver (as assessed by the central panel) according to CT scan obtained less than 2 weeks prior to registration, adequate tumour tissue available for assessment of *RAS* and *BRAF* mutation status, WHO performance status 0-1 (Karnofsky performance status ≥ 70), age ≥ 18 years, no contraindications for liver surgery, resectable primary tumour if still *in situ*, adequate organ functions, life expectancy over 12 weeks, expected adequacy of follow-up, and written informed consent.

Exclusion criteria are: previous systemic treatment for metastatic disease, extrahepatic metastases, with the exception of small (≤1 cm) extrahepatic lesions that are not suspicious of metastases, unresectable primary tumour, serious comorbidity or any other condition preventing the safe administration of study treatment (including both systemic treatment and surgery), major cardiovascular event within 12 months before randomisation, uncontrolled hypertension, or unsatisfactory blood pressure control with ≥3 antihypertensive drugs, previous adjuvant treatment unless completed ≥ 6 months prior to randomisation, previous surgery for metastatic disease, previous intolerance of study drugs in the adjuvant setting, pregnant or lactating women, second primary malignancy within the past 5 years with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin, any concomitant experimental treatment.

Panel procedure and evaluation

A central panel consisting of at least 3 liver surgeons and one radiologists will review the CT

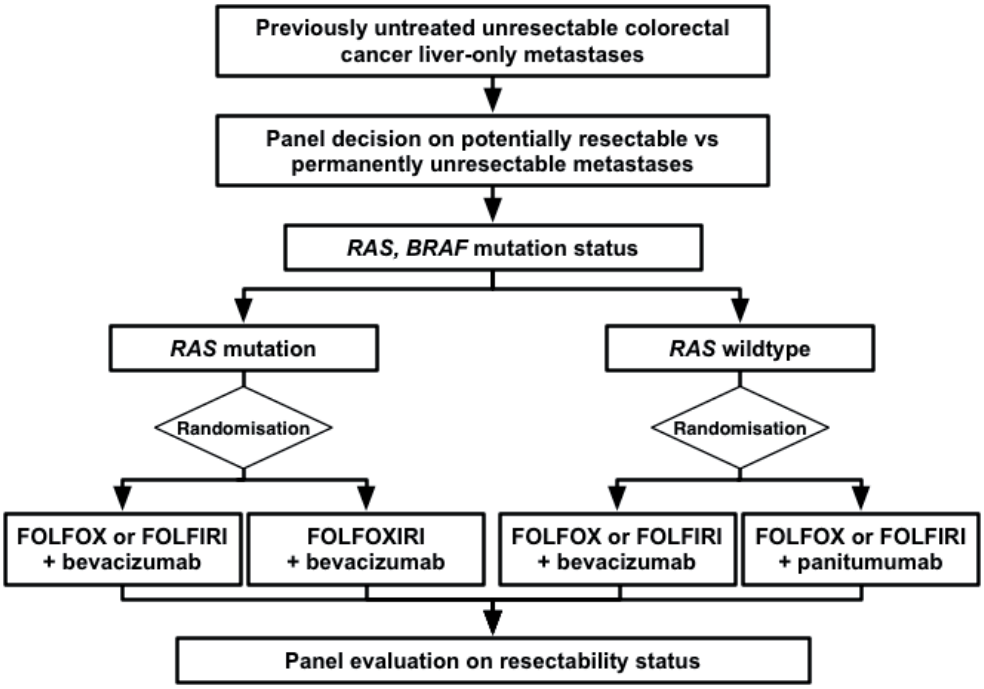


Figure 1. Study design CAIRO5

scans for resectability status prior to randomisation and at first evaluation (after 4 treatment cycles), and, if deemed necessary, at second evaluation (after 8 treatment cycles), and at third evaluation (after 12 treatment cycles). The central panel is blinded for the treatment arm. Any further review will take place according to panel decision.

By general consensus among Dutch hepatic surgeons, and for purpose of transparency and uniformity, unresectability *at baseline* for this study is defined as the expected failure of achieving a complete (R0) resection of all lesions in one single surgical procedure (i.e. excluding 2-stage resections, use of portal vein embolization) by surgical resection only (i.e. excluding the use of RFA or other surgical methods), leaving a minimum remnant liver volume of 25-30% in normal livers, and 35-40% in compromised livers (fibrosis, cirrhosis or steatosis).

Once a patient has entered the study following these criteria, the central panel will evaluate resectability of liver metastases after every 4 treatment cycles (now also allowing the use of preoperative portal vein embolization and the combination with local ablative techniques such as RFA, or of a two-stage resection). The decision of resectability will be made by the central panel by majority vote. The chairman of the panel will coordinate the voting process and confirm final decision of the panel. Secondary resection should include all lesions as demonstrated at baseline imaging, however, when lesions have disappeared under treatment and are not detectable during the surgical procedure, these will be left in

situ. The decision to perform secondary resection by laparoscopic or by open procedure is left to the discretion of the performing surgeon.

Patients' images will be uploaded in a software program specially designed to share patient imaging in a safe and privacy-respecting environment. (ALEA ®, FormsVision, Abcoude, the Netherlands)

Study treatment: systemic therapy

Patients will be treated according to the assigned treatment regimen. All systemic treatment regimens are administered according to standard practice, and all cycles have a length of 2 weeks. The choice between FOLFIRI and FOLFOX is at the discretion of the local investigator and may be selected on a per patient basis.

The assigned treatment will be continued for at least 6 months (12 cycles) or until progression of disease, unacceptable toxicity, or patient refusal. If after 6 months the liver metastases are still not resectable it is highly unlikely that resectability will be achieved at all. These patients have liver metastases that remain unresectable after induction systemic therapy, however without progression of disease. They should continue with the targeted drug in combination with chemotherapy, but the chemotherapy should be continued as maintenance treatment with 5FU/LV alone. The targeted drug should not be replaced by any other targeted drug during first-line treatment prior to disease progression.

Treatment after first progression is not part of the study, however recommended strategies can be found in the study protocol.

In patients who become resectable and undergo secondary surgery of their liver metastases, the total duration of preoperative and postoperative treatment together should be 6 months, with the chemotherapy schedule being continued postoperatively according to the preoperative schedule. However, given the lack of benefit of adding a targeted drug to chemotherapy in the adjuvant setting of stage III colon cancer [28-30] as well as of resected liver metastases [31], the targeted drug will not be continued after surgery.

Study statistics, sample size, planned analyses

The study is designed as a randomised phase 3 trial with progression free survival (PFS) as its primary endpoint. Two hypotheses will be tested simultaneously:

- in patients with *RAS* wild type tumours it is hypothesized that FOLFOX or FOLFIRI + panitumumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab.
- in patients with *RAS* mutant tumours it is hypothesized that FOLFOXIRI + bevacizumab will improve PFS as compared to FOLFOX or FOLFIRI + bevacizumab.

Given recent literature, it is expected that approximately 45% of the patients will have *RAS* (*KRAS* and *NRAS*) wild type tumours while 55% will have *RAS* mutated tumours.

The median PFS in patients with *RAS* wild type and *RAS* mutant tumours is estimated to be 10 months. The treatment is assumed to reduce the hazard rate for PFS by 30%. To detect such an improvement in PFS with 80% power and a two-sided logrank test at 5%, 247 events need to be observed. This requires an inclusion of approximately 640 patients, which are expected to be accrued in 4 years.

For the primary endpoint of PFS two interim analyses and a final analysis will be performed, equally spaced based on the number of events (approximately at one-third, two-third) of the way through the trial. At the interim analysis both futility and efficacy will be considered. The trial may be discontinued in either subgroup (RAS wild type and RAS mutated patients) when the treatment is very efficacious, but the trial may also be discontinued early in either subgroup if the new treatment is unlikely to show superiority to control based on the interim analysis.

Analysis of the primary endpoint will be based on the 'intention-to-treat' population. PFS by treatment arm will be calculated and depicted by means of the Kaplan Meier technique and will be compared using the (stratified) logrank test. Hazard ratios and 95% confidence intervals will be calculated with a (stratified) cox-proportional hazard analysis.

Quality

Data management will be centrally and locally provided by the clinical research department of the Comprehensive Cancer Center in the Netherlands (IKNL).

This study will be monitored based on the recommendations as described in the brochure "Kwaliteitsborging mensgebonden onderzoek 2.0" published October 2012 by the Dutch Federation of University Medical Centres (NFU). Independent qualified monitors, local and central oncology data managers of IKNL clinical research department, will monitor the trial.

Safety

In accordance to section 10, subsection 1, of the W.M.O. (Wet Medisch-wetenschappelijk Onderzoek met mensen), the investigator will inform the subjects and the reviewing accredited Medical Ethical Committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. It is mandatory to record and report all serious adverse event (SAEs). The local investigators are responsible for reporting SAEs. All SAEs must be reported within 24 hours. The DCCG as the initiator is responsible for SAE assessment and reporting to the authorities in accordance with all requirements of the Dutch law. The DCCG has delegated these responsibilities to the principal investigator of this study. The sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited Medical Ethical Committee, competent authority, and competent authorities of the concerned Member States.

In the CAIRO5 a Data Safety Monitoring Board (DSMB) is established to perform ongoing safety surveillance and to perform interim analyses on the safety data. This committee is an independent committee. The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Ethics

This study will be conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki (latest amendment), Dutch law in general and with the W.M.O. in particular.

The study has been approved by the medical ethical committee of the Academic Medical Centre Amsterdam, The Netherlands.

DISCUSSION

Secondary resection of liver metastases offers the only chance for cure in patients with initially unresectable, liver-only metastases. However data on secondary resection rates of initially unresectable colorectal cancer liver metastases are difficult to interpret. Most of these data are derived from retrospective studies, without data on outcome.

There are no data from prospective studies with transparent and uniform criteria for staging and resectability in patients with initially unresectable liver-only metastases. In the past, resectability of colorectal liver metastases has been based on tumour characteristics in the absence of extra-hepatic disease, such as the number of metastases, bilobar distribution, size of the largest metastasis and synchronicity. With improved treatment results and strategies these criteria have been modified. Currently, patients are selected on the basis of feasibility of achieving R0 resection with preservation of sufficient remnant liver to support metabolic liver function. Most surgeons will rely on a minimum of 25-30% of remnant liver, while maintaining adequate portal venous and hepatic arterial perfusion, hepatic venous drainage and biliary drainage.

Furthermore, based on the currently available data there is no outright preference for the use of either bevacizumab or anti-EGFR antibodies in combination with chemotherapy in patients with *(K)RAS* wild type tumours in whom secondary resection of metastases is the primary objective. Although its results are promising, triple chemotherapy with FOLFOXIRI has not shown to be outright superior in this respect to doublet regimens with FOLFOX or FOLFIRI.

In view of the considerations above, we elected to use clear-cut criteria for unresectability in the CAIRO5 study. Although by no means we consider these as the most optimal criteria,

the transparent and reproducible nature of these criteria do allow to select a homogeneous patient population in terms of liver involvement, which subsequently facilitates the interpretation of our data. This is further supported by the use of a central panel that prospectively evaluates the status of liver metastases according to these criteria in all patients. We expect that the results of the CAIRO5 trial will contribute to define the optimal strategy in patients with initially unresectable, liver-only colorectal cancer metastases. The study is open for accrual as of July 2014.

Competing interests

C.J.A. Punt has an advisory role for Roche, Amgen, Merck-Serono, Bayer, and Nordic Pharma. All the other authors have no competing interests.

Authors' contributions

CP and TG were responsible for the trial design and are the principal investigators, JH, TG and CP prepared the manuscript, JH is the trial coordinator, KL and ME the panel radiologists, GM and NG the coordinating pathologist, JS the trial consultant, AK and LM the central data managers, IM, CV, KP, CD, GK, TR, JW and TG are the panel liver surgeons and they contributed to the manuscript, HT is the trial statistician. All authors read and approved the final manuscript.

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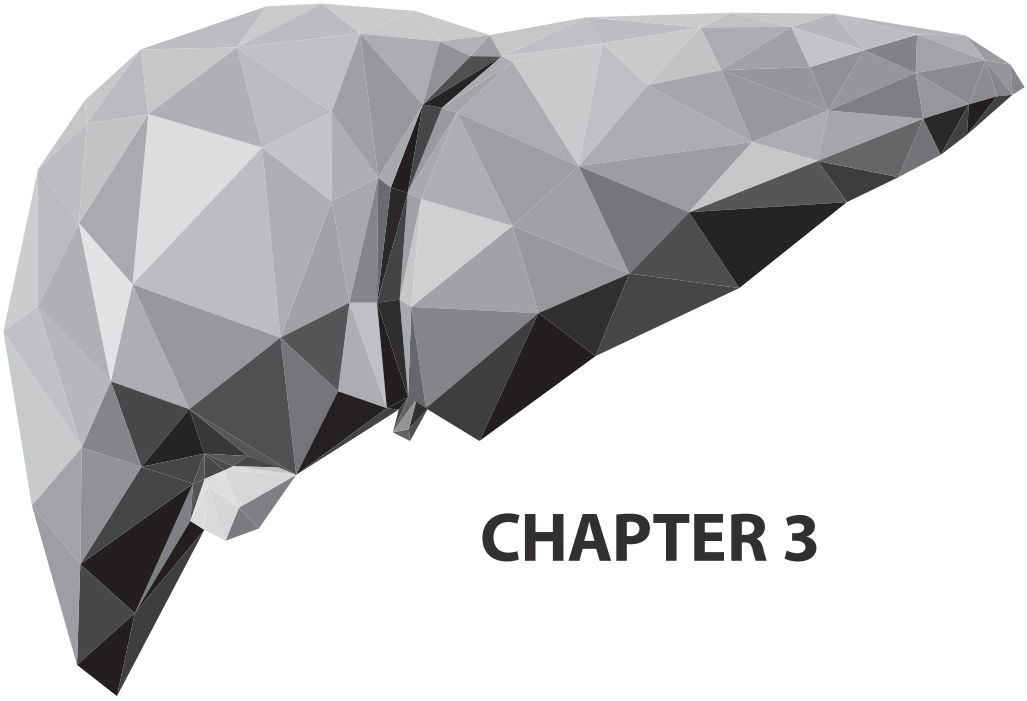

CHAPTER 3

Outcomes of resectability assessment of the Dutch Colorectal Cancer Group Liver Metastases Expert Panel

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ABSTRACT

Introduction

Decision making on optimal treatment strategy in patients with initially unresectable colorectal cancer liver metastases (CRLM) remains complex because uniform criteria for (un) resectability are lacking. The Dutch Colorectal Cancer Group (DCCG) Liver Expert Panel was established in conjunction with the CAIRO5 study; a multicenter, randomized, phase 3 trial investigating the optimal systemic induction regimen in patients with initially unresectable, colorectal liver-only metastases. All patients registered for the study, are prospectively evaluated for resectability by this panel of experienced hepatobiliary surgeons and radiologists according to predefined criteria. We hypothesized that the use of an expert panel may decrease individual subjectivity in defining (un)resectability and subsequently may improve consensus on criteria for resection and/or local ablative procedure of CRLM. This study reports on the feasibility and short-term outcomes of this Expert Panel.

Methods

The DCCG CAIRO5 Liver Expert Panel consists of thirteen hepatobiliary surgeons and four radiologists. Resectability assessment is performed independently by three randomly assigned liver surgeons through online evaluation. CRLM are scored as resectable, potentially resectable or permanently unresectable. In absence of consensus, two additional surgeons are invited for a majority consensus. Patients with potentially resectable or unresectable CRLM at baseline are evaluated after two months of systemic therapy and subsequently every two months as long as CRLM are considered as potentially resectable. Once CRLM are considered resectable, a treatment strategy is proposed.

Results

Overall, 398 panel evaluations in 183 patients were analyzed (183 baseline, 215 follow-up). The median time to panel conclusion was 7 days (IQR 5-11). Inter-surgeon disagreement was observed in 205 (52%) evaluations, with major disagreement (resectable vs permanently unresectable) in 42 (11%) evaluations. After systemic treatment, 106 patients were considered to have resectable CRLM, out of which 84 (79%) patients underwent a surgical and/or a local ablative procedure. R0 resection (n=41) or R0 resection in combination with ablative treatment (n=26) or ablative treatment only (n=4) was achieved in 67/84 (80%) patients.

Conclusion

This study analyzed prospective resectability evaluation of patients with CRLM by a panel of radiologists and liver surgeons. The high variation in judgment among experienced liver surgeons reflects the complexity in defining treatment strategies for CRLM and supports the use of a panel rather than a single-surgeon decision.

INTRODUCTION

Survival rates in patients with metastatic colorectal carcinoma (CRC) have increased over the past decades owing to the increased resection rate of metastases and the development of effective systemic drugs. In 30-40% of patients, CRC metastases are limited to the liver.[1,2] Resection of colorectal liver metastases (CRLM) offers the chance of long-term disease-free survival or cure, with 5-year survival rates after resection ranging between 25% and 58%.[3–5] In addition to standard, one-stage resections, several other options are currently available to achieve clearance of the liver from all tumors. The combination of resection with local ablative techniques enables sparing of parenchyma and preoperative portal vein embolization can be used to induce hypertrophy of the future liver remnant rendering patients with upfront too small liver remnant amenable to resection.[6] Two-stage hepatectomy and Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) are strategies to allow extensive resections in patients with bilobar metastases. Despite these novel techniques, only the minority of patients with CRLM (20%) present with metastases deemed resectable upfront.[7,8] In patients with upfront unresectable CRLM, a number of studies have shown that downsizing of CRLM by induction systemic treatment may allow secondary resections with survival rates similar to primary resections.[9–11]

The lack of criteria for (un)resectability in most studies induces selection bias and thereby complicates the interpretation of patient outcomes. Historically, the number and size of CRLM and 1 cm resection margins were the dominant criteria that were used to define (un) resectability. These criteria have gradually been abandoned, because multiple studies have shown significant survival benefits of liver resection even in patients with very advanced CRLM.[12,13] Currently, the main issue is whether a complete resection with tumor-free margins is feasible while preserving at least 20-30% of total liver volume, with adequate vascular in- and outflow and biliary drainage.[14] To enable adequate assessment of resectability, the presence of at least one experienced liver surgeon in a dedicated multidisciplinary team conference is considered mandatory.[15,16] The criteria for resectability are however, subject to individual interpretation.[17,18] Although there may exist consensus on the extremes of upfront resectable versus permanently unresectable CRLM, large interobserver variability concerning resectability has been observed even among experienced liver surgeons.[19–22]

The ongoing CAIRO5, multicenter, randomized, phase 3 trial of the Dutch Colorectal Cancer Group (DCCG) investigates the optimal systemic induction regimen in patients with initially unresectable, colorectal liver-only metastases.[23] An innovative aspect of the study design is that all patients are prospectively evaluated for resectability by an expert panel consisting of experienced hepatobiliary surgeons and radiologists according to predefined criteria. We hypothesized that the use of such a panel may decrease individual subjectivity in defining (un)resectability and subsequently may improve consensus on criteria for resection of CRLM.

This study analyses the outcomes and feasibility of the CAIRO5 national DCCG Liver Expert Panel in resectability assessment for patients with CRLM at baseline and during induction systemic treatment.

METHODS

Patients

All patients registered between November 2014 and August 2017 in the ongoing CAIRO5 study; a multicenter, randomized, phase 3 trial of the DCCG (EudraCT 2013-005435-24, ClinicalTrials.gov: NCT02162563) were selected for this analysis.[23] The CAIRO5 study randomizes patients with unresectable or potentially resectable CRLM and no extrahepatic metastases in 1) doublet chemotherapy plus either bevacizumab or panitumumab for left sided primary, *RAS* and *BRAF* wildtype tumors, or 2) doublet or triplet chemotherapy, both with bevacizumab for *RAS* or *BRAF* mutated tumors or right sided primary tumors. Patients were evaluated for resectability by the panel at baseline and during systemic treatment. The following outcome parameters were recorded: time required by the expert panel to reach a panel conclusion, inter-surgeon variation on resectability assessment, and adherence to the panel recommendation for local treatment by the collaborating center.

Patient imaging

Tumor staging and response analysis were assessed using contrast enhanced, abdomen-pelvic CT scan and thoracic helical CT scan or a conventional thoracic radiograph at baseline and every 8-9 weeks after baseline imaging. Use of MRI of the liver or PET scan was left to the discretion of the local treatment team, since these imaging modalities were not mandatory according to the Dutch colorectal cancer guideline. If results of these studies were available and showed additional information concerning the metastases, these scans were uploaded and reviewed by the expert panel as well.

Predefined resectability criteria

For the purpose of transparency and homogeneity of the trial population and to reduce selection bias, consensus among liver surgeons was achieved on criteria for initial (un) resectability during a meeting of the Dutch Liver Surgery working group.[24] Resectability at baseline was defined as the ability to obtain a complete (R0) resection of all lesions in one single surgical procedure (i.e. excluding 2-stage resections and/or use of portal vein embolization) by resection only (i.e. excluding the use of additional ablative treatments or other local methods), leaving an estimated minimum remnant liver volume of 25-30% in uncompromised livers, or 35-40% in compromised livers prior to treatment (fibrosis, cirrhosis or steatosis). Options for local treatment during induction systemic therapy

included 2-stage resections, use of preoperative PVE, ALPPS, and combinations with local ablative treatments.

Design of the DCCG Liver Metastases Expert Panel

The DCCG Liver Expert Panel consists of 13 liver surgeons and 4 radiologists from 12 hospitals. The liver surgeons are all member of the Dutch Study Group for Liver Surgery, have extensive experience in treating patients with CRLM. All liver surgeons are part of a local surgical team that performs more than 20 liver resections per year.[25]

A digital online platform was designed that allowed uploading of the images by the local hospital and the independent assessment of resectability by each panel member (ALEA®, FormsVision, Abcoude, The Netherlands).

CT Scans were digitally anonymized and reviewed by a panel radiologist. The radiologist evaluated metastases according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1. When the panel radiologist confirmed that no extrahepatic metastases were present, three liver surgeons were randomly selected. Based on the available imaging studies and the accompanying radiology report, all three panel surgeons individually voted on resectability by choosing one of the following three categories: 1) resectable 2) potentially resectable, or 3) permanently unresectable. In case CRLM were considered to be potentially resectable, the panel surgeons were requested to differentiate between a) technically unresectable but potentially resectable after (further) downsizing and b) technically resectable but start/continuation of systemic treatment is preferred. If no consensus was reached among the three panel surgeons, two additional panel surgeons were randomly selected to evaluate resectability. Minor disagreement is defined as: a panel evaluation in which one of the panel surgeons assessed the CRLM as potentially resectable and one other surgeon in the same panel assessed the CRLM as resectable or permanently unresectable. Major disagreement is defined as: a panel evaluation in which at least one of the panel surgeons assessed the CRLM as resectable and another surgeon in the same panel voted for permanently unresectable CRLM. The final decision on resectability was made according to the majority of votes among the selected panel members. The chairman of the panel, who is not one of the voting members, coordinated the voting process, confirmed the final decision of the panel and strived for a panel conclusion within 14 days. One central study coordinator (JH, KB) monitored the progress of the evaluation and solved problems such as questions from the participating hospitals or technical problems experienced by the panel members. The logistics of the panel is schematically represented in Figure 1.

To confirm unresectability of CRLM, panel evaluation was performed at baseline prior to randomization and after every eight weeks, equal to four treatment cycles. At baseline, patients with CRLM assessed as resectable, did not qualify for inclusion in the CAIRO5 study. At follow-up evaluations, further resectability assessments were discontinued when CRLM were assessed as permanently unresectable or resectable. In case CRLM were considered

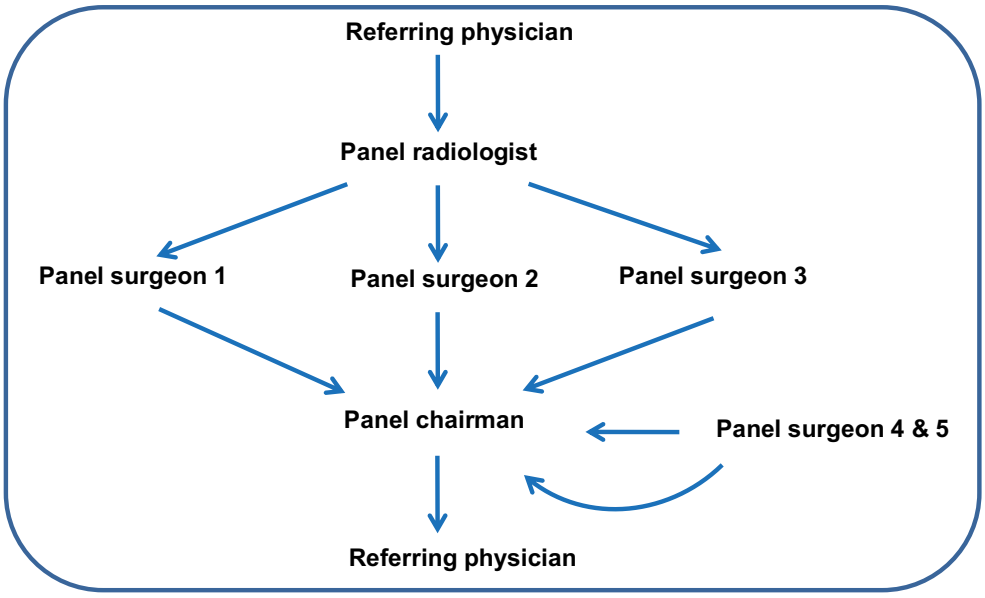

Figure 1. Logistics of resectability assessment by DCCG Liver Expert Panel

resectable, the local treatment team was notified and a surgical plan was proposed. All patients assessed as having potentially resectable CRLM at first follow-up evaluation, corresponding to four treatment cycles, are re-evaluated after eight treatment cycles at 16 weeks and, if still considered potentially resectable, for a final assessment after 12 treatment cycles at 24 weeks.

To evaluate the feasibility and predictive accuracy of the panel conclusions, clinical outcomes in terms of resection rate, type of resection with adjunctive use of local additional modalities (ablative treatments, PVE, 2-stage resection, ALPPS) and R0 resection rate were analyzed. Reasons for deviation from panel conclusions were documented.

Outcomes of resections were evaluated by type of resection as well as the R0 resection rate. R0 resection was defined as microscopically margin-negative resection, in which no microscopic tumor cells have remained in the resection margins of surgically removed metastases. R1 resection indicates the removal of all macroscopic disease, but microscopic margins are positive for tumor cells. In case only local ablative treatment was performed, no R status could be defined. The local physician judged the local ablative procedure to be complete or incomplete. Discrepancies between the local treatment plan proposed by the DCCG Liver Expert Panel and the actual treatment procedures were also documented.

The design of the DCCG Liver Expert Panel including the procedure of assessment was part of the study protocol and approved by the Institutional Review Board of the Amsterdam UMC.

The proposed surgical plan for patients with CRLM assessed as resectable at follow-up, should attempt to include all lesions as demonstrated at baseline imaging. However, pretreatment lesions in complete radiological remission and not detectable during surgery were left *in situ*. The decision to perform resection by laparoscopic or by open procedure was left to the discretion of the performing surgeon.[26]

Patients with synchronous metastatic disease were eligible for study participation in case the primary tumor was deemed resectable by the local MDT or after succesful recovery from immediate surgery for symptoms such as obstruction or bleeding. Patients with a primary tumor in situ and in which the liver metastases became resectable should receive subsequent surgical treatment for the primary tumor. Timing and type of procedure of primary tumor was left to the discretion of the local MDT, according to standard guidelines.

Statistical analysis

Continuous variables were displayed as median with inter-quartile-range (IQR) and categorical variables by number with percentages. Categorical variables were analyzed using chi-square test. Statistical analyses were performed using SPSS 25.0 (IBM, Chicago, IL). Chi-square tests were two-tailed and $p < 0.05$ was considered significant.

RESULTS

Between June 2014 and August 2017, 200 patients with CRLM from 41 Dutch hospitals were registered and screened for eligibility for the CAIRO5 trial (Figure 2). Of these patients, 17 were found to be ineligible for study participation at registration prior to panel evaluation: 13 patients did not meet the inclusion criteria of whom seven had extrahepatic metastases, and four patients withdrew from participation before panel conclusion at baseline was reached.

Evaluation of resectability

Overall, 398 panel evaluations in 183 patients were analyzed (183 baseline, 215 follow up evaluations). At baseline, 10 patients were assessed to have initially resectable CRLM. These patients were considered ineligible for participation in the CAIRO5 study. The panel conclusion along with the proposed surgical plan was forwarded to the referring treatment team. The remaining 173 patients were assessed as having initially unresectable CRLM, of which 127 potentially resectable and 46 permanently unresectable CRLM. Of the 173 patients with initially unresectable CRLM, six patients were not re-evaluated at first follow-up, Reasons patients were not re-evaluated are presented in Figure 2.

At first follow up evaluation (FU1), 73 of 167 (45%) patients were considered to have resectable CRLM, 48 (29%) permanently unresectable and 46 (28%) potentially resectable

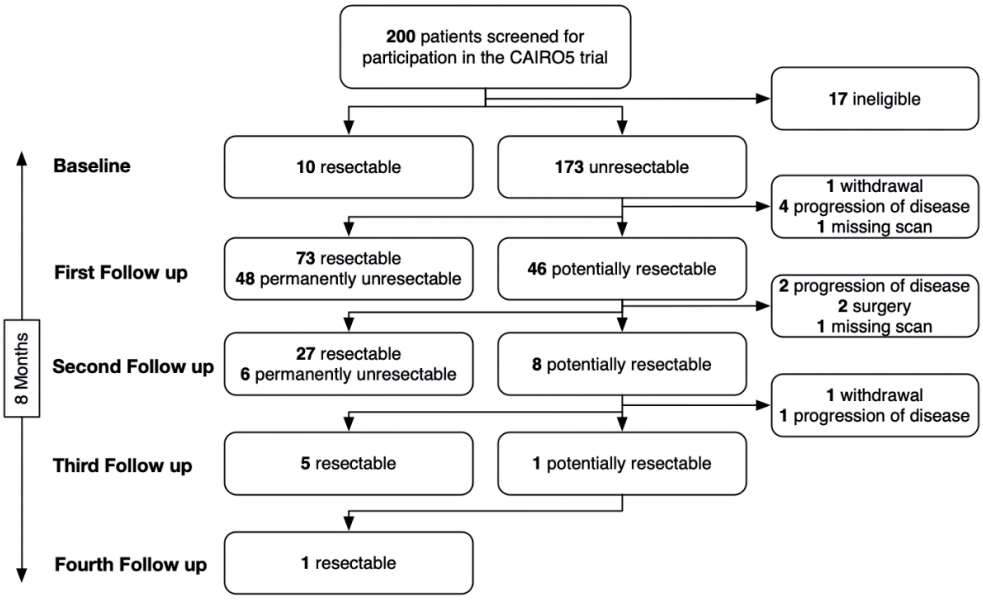

Figure 2. Flowchart with numbers of patients assessed to be resectable, potentially resectable or permanently unresectable at baseline, and follow up evaluations and reasons for patients not to be re-evaluated.

CRLM. In patients with potentially resectable CRLM, systemic treatment was continued with a panel evaluation after four more cycles of systemic therapy. Five of 46 (11%) patients with CRLM considered as potentially resectable at FU1 were not re-evaluated by the panel at second follow-up evaluation (FU2), leaving 41 patients for second follow-up evaluation (FU2).

At FU2, 27 of 41 (66%) patients were considered to have resectable, 6 (15%) permanently unresectable and 8 (20%) potentially resectable CRLM. At FU3, 5 of 6 patients (83%) were considered to have resectable CRLM while in one patient the scan showed ongoing response with still extensive CRLM. In this case the panel preferred to continue systemic treatment for another four cycles, i.e. for a total of eight months. At fourth follow-up evaluation (FU4), the CRLM of this patient were considered resectable. (Figure 2 and 3)

Conversion rate

Of 127 patients with CRLM assessed as potentially resectable at baseline evaluation, 71 (56%), 24 (19%) and 4 (3%) patients were converted to resectable disease after systemic induction therapy at FU1, FU2 and FU3, respectively. CRLM were considered permanently unresectable in 13 (10%) and 5 (4%) patients at FU1 and FU2, respectively. Thirty-six (78%) of 46 patients considered to have permanently unresectable CRLM at baseline, remained permanently unresectable during follow-up assessment, whereas 2 (4%), 3 (7%), 1 (2%) and 1 (2%) patients converted from permanently unresectable disease to resectable disease at FU1, FU2, FU3 and FU4, respectively.

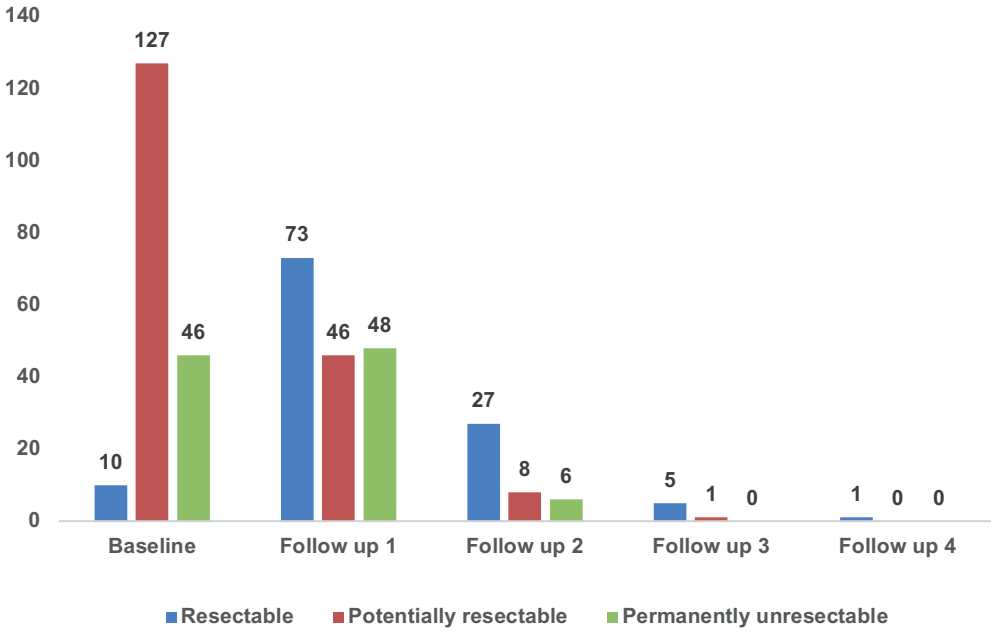

Figure 3. Distributions of panel conclusions at baseline and during follow up

Time to panel conclusion

Overall, the median time to panel conclusion was 7 days (IQR 5-11). At baseline and follow-up evaluations, the median time to panel conclusion was 6 days (IQR 4-9 days) and 9 days (IQR 6 – 13 days), respectively.

Inter-surgeon variation in panel evaluations

Overall, any form of inter-surgeon disagreement was observed in 206 (52%) baseline and follow up evaluations, with major disagreement (resectable vs permanently unresectable) in 42 (11%) evaluations. Any inter-surgeon disagreement was lower at baseline compared to follow-up panel evaluations; 80 (43.7%) versus 126 (58.6%), respectively , $p = 0.003$. Major inter-surgeon disagreement was lower at baseline compared to follow-up panel evaluations; 3 (1.6%) vs 39 (18.1%), respectively, $p < 0.001$.

At FU1, FU2 and FU3, in 69 (41%), 19 (47%) and 1 (17%) patients all panel members agreed on the treatment plan. Major panel disagreement was present at baseline, FU1, FU2 and FU3, in 3 out of 183 (2%), in 24 of 167 (14%), in 12 of 41 (29%) and in 3 of 6 (50%) panel evaluations, respectively. (Table 1)

Over time the number of evaluations with panel disagreement increased. In the first 199 panel evaluations, panel disagreement existed in 91 (46%) of evaluations compared to 115 (58%) in the second group, defined by the last 199 panel evaluations ($p = 0.021$).

Table 1. Inter-surgeon variation in panel evaluations

	Panel agreement	Minor disagreement*	Major disagreement**
Overall, n (%)	**193 (48)**	**163 (41)**	**42 (11)**
Baseline, n (%)	103 (56)	77 (42)	3 (2)
Follow up 1, n (%)	69 (41)	74 (45)	24 (14)
Follow up 2, n (%)	19 (47)	10 (24)	12 (29)
Follow up 3, n (%)	1 (17)	2 (33)	3 (50)
Follow up 4, n (%)	1 (100)	0 (0)	0 (0)

**In one panel evaluation at least at least one panel surgeon judged "potentially resectable" whereas at least one other surgeon judged "permanently unresectable or "resectable"*
*** In one panel evaluation at least one panel surgeon judged "resectable" whereas at least one other surgeon judged "permanently unresectable"*

Adherence to panel conclusion

Of 10 patients with CRLM considered resectable at baseline, who did not receive systemic therapy in the CAIRO5 study, 2 patients underwent R0 resection while 5 patients first started systemic treatment upon decision of the local surgeon or MDT and in 3 patients extrahepatic metastases were found on additional imaging.

A total of 106 (61%) patients with initially unresectable CRLM (73 patients at FU1, 27 at FU2, 5 at FU3 and 1 patient at FU4) were assessed as having resectable CRLM at follow up evaluation. In 93 (88%) of these patients, resection of CRLM was attempted. Complete local treatment of CRLM by resection (n = 51) or resection in combination with ablative therapy (n = 29) or ablative therapy only (n = 4) was performed in a total of 84 (79%) patients. Reasons for not performing surgery or local treatment despite the advice of the liver panel are presented in table 2. In 38% of resections and/or local ablative treatments, the final procedure was carried out exactly similar to the treatment plan suggested by the panel.

Characteristics of the intervention in patients that underwent resection and/or local ablative treatment

Out of 84 patients that underwent a procedure with curative intent, 21 (25%) patients required preoperative portal vein embolization. Twenty-seven (32%) patients underwent a right hemihepatectomy, 21 (25%) a segmentectomy or local resection plus ablative treatment, 17 (21%) a segmentectomy or local resection, 7 (8%) a left hemihepatectomy, another 7 (8%) an extended right hemihepatectomy, 4 (5%) patients were treated with a local ablative procedure only and 1 patient underwent an extended left hemihepatectomy. Twenty-two (26%) two-stage procedures and 11 (13%) laparoscopic procedures were performed (Table 3).

In patients who underwent resection (n=51), R0, R1 and R2 resections were achieved in 41 (80%), 9 (18%) and 1 (2%) cases, respectively. In patients who underwent resection in combination with local ablative treatment (n=29), R0, R1 and R2 resections were achieved in 22 (76%), 6 (21%) and 1 (3%) cases, respectively.

Table 2. Adherence to panel conclusion and panel treatment plan in resectable patients at follow up evaluation

All, n	**106**
Resection and/or local ablative treatment, n (%)	
- Yes	84 (79)
- No	22 (21)
Reason no resection and/or local ablative treatment	
- Perioperatively unresectable (open-close)	*6*
- Condition patient	*4*
- Decision local surgeon/MDT	*4*
- New intra- and/or extrahepatic metastases	*4*
- 2nd stage not executed due to insufficient liver remnant	*3*
- Decision patient	*1*
Final resection similar to panel treatment plan, n (%)	
- Yes	32 (38)
- No	52 (62)
Reasons resection not similar to panel conclusion	
- Final resection more extensive	*12*
- Final resection less extensive	*16*
- 1-stage- converted to 2-stage resection	*8*
- 2-stage- converted to 1-stage resection	*7*
- Local ablative treatment instead of wedge/segment resection	*8*
- Wedge/segment resection instead of local ablative treatment	*1*

Table 3. Procedure characteristics

All, *n*	**84**
Portal vein embolization, *n (%)*	
- Yes	21 (25)
- No	63 (75)
Surgical and/or ablative treatment, *n (%)*	
- Surgical procedure	51 (60)
- Surgical + local ablative treatment	29 (35)
- Local ablative treatment	4 (5)
Type of procedure, *n (%)*	
- Left hemihepatectomy	7 (8)
- Extended left hemihepatectomy	1 (1)
- Right hemihepatectomy	27 (32)
- Extended right hemihepatectomy	7 (8)
- Segmentectomy/local resection	17 (21)
- Segmentectomy/local resection + Local ablative treatment	21 (25)
- Only Local ablative treatment	4 (5)
Two stage procedures, n (%)	
- Yes	17 (20)
- ALPPS	5 (6)
- No	62 (74)
Laparoscopic procedure, *n (%)*	
- Yes	11 (13)
- No	70 (83)
- Unknown	3 (4)
Radicality, *n (%)*	
- R0	63 (75)
- R1	15 (18)
- R2	2 (2)
- Local ablative treatment only	4 (5)

Outcome in relation to panel agreement

Out of 106 patients evaluated to have resectable CRLM, 52 (49%) patients had assessments with panel agreement whereas in 54 (51%) patients panel disagreement occurred. In patients with panel agreement and resectable CRLM, resections (26) and/or ablative treatment (19) was undertaken in 45 of 52 (87%) patients, whereas 39 of 54 (72%) patients received resections (25) and/or ablative treatments (14) when there was panel disagreement at evaluation (p = 0.069). In patients with panel agreement, R0 resection (22) and/or ablative treatment (17) was achieved in 39 out of 52 (75%) patients, compared to 28 (19 resections and 9 resections with ablative therapy) out 54 (52%) patients (p = 0.013) when disagreement occurred.

In panel evaluations with major panel disagreement and resectable outcome, 9 of 18 (50%) patients did not receive a liver resection. The reasons for non-resection in this group included: intraoperative unresectability in 3 patients, insufficient future liver remnant in 2, decision overruled by the local MDT or surgeon in 3 and decision of the patient in 1.

Further analysis was done excluding 13 patients in whom no surgery was initiated for reasons of extrahepatic disease, decision of local MDT or condition of the patient. Of the remaining 93 patients, 47 (51%) had an assessment with panel agreement. R0 resection (22) and/or local ablative treatment (17) was achieved in 39 out of 47 (83%) patients with panel agreement, compared to 28 (19 resections and 9 resections with ablative therapy) out 46 (61%) patients with panel disagreement (p = 0.018) (Table 4).

DISCUSSION

This study demonstrates successful implementation and feasibility of the CAIRO5 national DCCG Liver Expert Panel in clinical practice. The median time to panel conclusion of 7 days was considerably faster than the preconceived maximum of 14 days allowing efficient assessment by multiple experienced liver surgeons in these very complex patients.

Despite resectability assessments by a panel of experienced liver surgeons, a high level of inter-surgeon disagreement per assessment was observed, as shown in earlier studies.[17–19,21] This underlines the complexity of defining (un)resectability. However, with consensus on baseline criteria for (un)resectability, we noted significantly less inter-surgeon variation compared to follow-up evaluations, which underscores the value of well-defined resection criteria. Our data supports the evaluation of CRLM patients by a panel of liver surgeons rather than by an individual surgeon or MDT in order to achieve a more reproducible and more balanced decision per patient. The true value of the panel can be assessed when further clinical, translational and outcome data are available. The high R0 resection rate and / or ablative treatment rate after patients were considered resectable, confirms the feasibility of resectability assessment by the panel. The difference in successful

Table 4. Outcome in relation to panel agreement in patients with CRLM considered resectable by the panel after systemic therapy.

	Total patients with resectable CRLM n=106 (100%)	**Panel agreement n=52 (100%)**	**Panel disagreement n=54 (100%)**	***P value***
	n (%)	n (%)	n (%)	
Resection without ablative treatment				
R0	41 (39)	22 (42)	19 (35)	
R1	9 (8)	3 (6)	6 (11)	
R2	1 (1)	1 (2)	0 (0)	
Resection with ablative treatment				
R0	22 (21)	13 (25)	9 (17)	
R1	6 (6)	1 (2)	5 (9)	
R2	1 (1)	1 (2)	0 (0)	
Local ablative treatment only	4 (4)	4 (8)	0 (0)	
Perioperatively unresectable	6 (6)	2 (4)	4 (7)	
2nd stage not done, insufficient liver remnant	3 (3)	0 (0)	3 (6)	
No surgery	13 (12)	5 (10)	8 (15)	
Resection and/or ablative treatment	84 (79)	45 (86)	39 (72)	*0.069*
No resection and/or ablative treatment	22 (21)	7 (14)	15 (28)	
R0 resection and/or ablative treatment	67 (63)	39 (75)	28 (52)	*0.013*
R1 or R2 or incomplete or no resection	39 (37)	13 (25)	26 (48)	

local treatment (R0 resection and/or ablative treatment) between patients with evaluations with panel agreement versus panel disagreement shows resectability is more difficult to predict in this subgroup of patients and calls for the definition of more stringent resectability criteria. The design of this panel enables further prospective analysis of these subgroups, incorporating follow-up data on clinical outcomes and translational research data on clinical characteristics and biomarkers, in order to provide improved selection criteria for (un) resectability. The increase over time of panel evaluations with disagreement, confirms lack of resection criteria remains an important issue today and that the outcomes of these future analyses are as vital as when the CAIRO5 study started in 2014.

In 62% of patients, the final resection carried out was different from the surgical plan proposed by the panel. We assign this high rate to the fact that the surgical plan itself was

not mandatory. Other explanations could be that most hospitals perform an additional preoperative MRI because of better diagnostic performance and the finding of new lesions.[27–29] Furthermore, intraoperative adjustment of the surgical plan is a well-known phenomenon since intraoperative ultrasonography is still known to be the golden standard in revealing the total extent of the disease.[30–32] We did not note much resistance from local MDTs or surgeons regarding the proposed treatment plans by the panel. Two patients with potentially resectable CRLM as assessed by the panel, did not finish further panel evaluations because the local surgeon or MDT decided to proceed with surgical resection. In four patients considered resectable by the panel, the resection was not executed due to disagreement of the local surgeon or MDT.

In the absence of formal international consensus on resectability criteria for CRLM, baseline criteria for unresectability were defined by consensus among Dutch liver surgeons for the purpose of more uniform selection of CRLM patients for multimodality treatment according to state-of-the-art management of CRLM in a governed, auditable and reproducible manner, allowing improved reproducibility and minimal selection bias in the CAIRO5 study, as well as a better interpretation of patient outcomes.[23]

Our criteria imply that more patients are exposed to perioperative systemic treatment in the CAIRO5 study than in routine Dutch practice, since (neo)adjuvant systemic therapy is not recommended in the Dutch treatment guidelines for patients with resectable CRLM due to the lack of survival benefit in the EPOC trial.[33] This will have contributed to the high conversion rate of 61%. However, there was general consensus that the administration of induction systemic treatment is ethical and appropriate in the relatively high-risk patient group qualifying for the CAIRO5 study, moreover because some studies suggest a survival benefit of systemic therapy in patients with high risk CRLM.[34–36]

This study has possible limitations. Evaluation of the panel is by observational design, which could introduce bias. However, a randomized selection for evaluation by the panel was considered unethical. Lastly, the evaluation of patients was performed only by radiological imaging, without individual information of a patient's clinical condition and comorbidity. Though, the CAIRO5 eligibility criteria included the most relevant assessments of performance status and organ functions to allow the safe administration of systemic treatment and surgery.

CONCLUSION

This study analyzed prospective evaluation of patients with unresectable CRLM as defined by uniform criteria using an online expert panel of radiologists and liver surgeons. The high inter-surgeon variation reflects the complexity in defining treatment strategies for CRLM and supports the use of a panel rather than a single-surgeon decision. Our results

demonstrate that the DCCG CAIRO5 Liver Expert Panel is feasible and provides a platform for prospective initial and follow-up assessments on resectability in patients with advanced CRLM on a national level.

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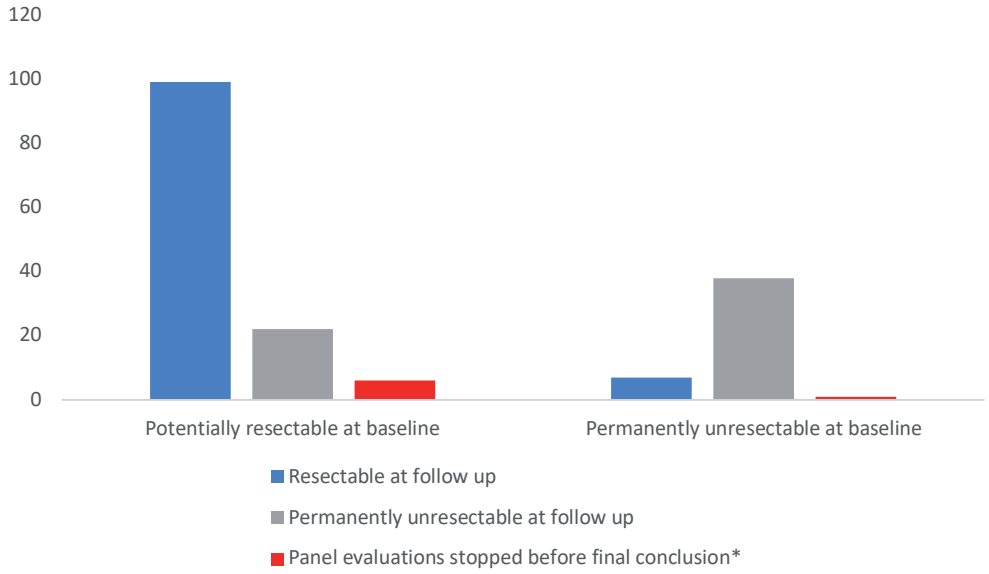
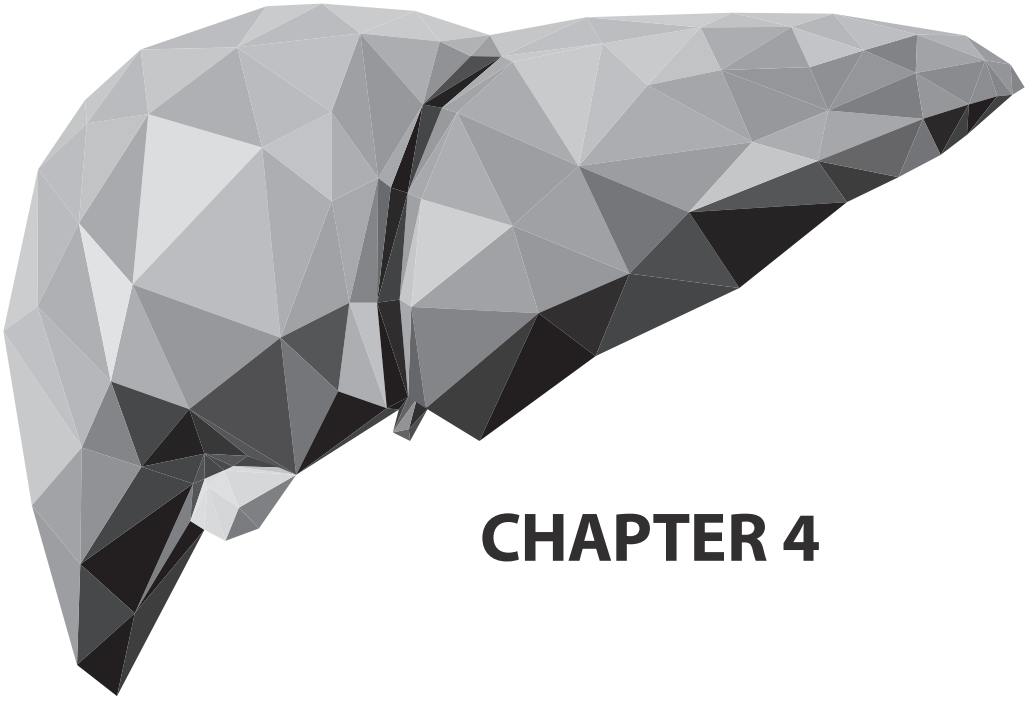


* Patients with missing panel evaluations because of progression were scored as permanently unresectable

Figure S1. Distributions of panel conclusions at follow up according to panel conclusion at baseline



CHAPTER 4

Does portal vein embolization prior to liver resection influence the oncological outcomes – a propensity score matched comparison

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ABSTRACT

Introduction

There is an ongoing controversy surrounding portal vein embolization (PVE) regarding the short-term safety of PVE and long-term oncological benefit. This study aims to compare survival outcomes of patients subjected to major liver resection for colorectal liver metastases (CRLM) with or without PVE.

Methods

All consecutive patients who underwent major liver resection for CRLM in four high volume liver centers between January 2000 and December 2015 were included. Major liver resection was defined as resection of at least three Couinaud liver segments. To reduce selection bias, propensity score matching was performed for PVE and non-PVE patients with overall and disease-free survival as primary endpoints. For matching, all patients who underwent PVE followed by a major liver resection were selected. Patients were matched to patients who had undergone major liver resection without PVE.

Results

Of 745 patients undergoing major liver resection for CRLM, 53 patients (7%) underwent PVE before liver resection. In the overall cohorts, PVE patients had inferior DFS and a trend towards inferior OS. A total of 46 PVE patients were matched to 46 non-PVE patients to create comparable cohorts and between these two matched cohorts no differences in DFS (3-year DFS 16% vs 9%, $p = 0.776$) or OS (5-year OS 14% vs 14%, $p = 0.866$) were found.

Conclusions

This retrospective, matched analysis does not suggest a negative impact of PVE on long-term outcomes after liver resection in patients with CRLM.

INTRODUCTION

Postoperative liver failure is a severe complication after liver resection and is the most important cause of death after liver surgery.[1,2] Since, the incidence of postoperative liver failure is directly related to the volume of the future liver remnant (FLR),[3–6] , liver surgery is only considered safe if the FLR consists of at least 20-30% of the total liver volume.[7] Preoperative portal vein embolization (PVE) is a technique in which one side of the portal venous system is occluded to induce hypertrophy of the contralateral liver lobe. PVE is currently considered the golden standard to preoperatively increase the FLR when it's volume is less than 20-30% in order to decrease the risk of liver failure.[8,9]

There is an ongoing controversy whether PVE may induce the induction of tumour progression in the interval between PVE and resection.[10] Most patients subjected to PVE proceed to liver resection, however in 18-40% of these patients no resection is performed, mostly due to unresectable tumour progression. In patients with colorectal liver metastases (CRLM) overall tumour progression is reported in 21-66% of patients after PVE.[11–15] The prognostic significance of the observed tumour progression after PVE remains unclear. Overall 5-year survival of CRLM patients undergoing major hepatectomy after PVE ranges from 21 to 46%.[12,13,16,17] Disease-free survival has been reported to be compromised in patients after PVE and resection, however these series are subject to selection bias which hampers comparison with non-PVE patients. In several comparative reports PVE patients had a higher tumour load and therefore unfavourable prognostic characteristics which could confound the reported outcomes when compared to patients who did not underwent PVE.[16]

This study aims to compare survival outcomes of patients subjected to major liver resection for CRLM with or without PVE. To reduce the selection bias, patients who underwent PVE were matched to non-PVE patients using propensity score matching with overall and disease-free survival as primary endpoints.

MATERIALS AND METHODS

Patients

All consecutive patients who underwent major liver resection for CRLM at four high volume-centres (Erasmus Medical Center, Academic Medical Center, Radboud University Medical Center, and Maxima Medical Center) between January 2000 and December 2015 were included. The inclusion criteria was curative intent of liver resection of at least three Couinaud liver segments.[18] Patients who underwent radiofrequency ablation (RFA) were included only if the performed resection without the RFA classified as a major resection. Exclusion criteria included two-stage liver resections and patients with alternative diagnoses at pathologic examination. Patients who did not undergo any further surgery after PVE due

to tumour progression or insufficient hypertrophy response of the FRL were excluded in our analysis. The study protocol was considered by the institutional review board and no ethical approval was required. The need for individual informed consent was waived.

Patient workup

Treatment strategy for all patients was discussed in a multidisciplinary meeting including surgeons, medical oncologists, gastroenterologist, radiotherapists, and radiologists. Neoadjuvant downsizing systemic therapy was considered in patients with initially unresectable CRLM. According to the Dutch guidelines for colorectal cancer treatment, (neo)adjuvant systemic therapy is not indicated in patients with upfront resectable CRLM. PVE was considered based on liver volume measurements, with 25% considered as a safe remnant liver volume to proceed with resection. PVE was generally performed using the contralateral approach and embolization was done with poly-vinyl alcohol particles, platinum coils, Amplatzer plugs, glue and/or gelfoam at the discretion of the interventional radiologist. Volume measurements using contrast-enhanced computed tomography (CT) imaging were generally repeated 3-4 weeks after PVE and interval systemic therapy between PVE and surgery was not common practice.

Standard follow-up included hepatic ultrasonography or abdominal CT combined with thoracic imaging (X-ray or CT) every 3-6 months until 2 years after surgery and 6-12 months thereafter. Serum CEA was measured every 3-6 months. Resectable recurrences were considered for repeat resection. Patients with unresectable recurrence were referred for palliative systemic therapy. Adjuvant systemic therapy is not part of Dutch clinical practice guidelines because of the lack of an overall survival benefit.

Variables

Study variables included characteristics of the primary tumour including staging and origin. The characteristics of the hepatic metastases included the number of lesions, the diameter of the largest metastases, synchronous or metachronous presentation (12-month interval), serum CEA level, and the type of resection performed. Resection of multiple segments with or without addition of radiofrequency ablation or wedge resections were classified as segmentectomy. Any addition to a left or right hepatectomy was defined as extended resection.

Complications were scored and classified according to the Clavien-Dindo classification within 30 days after surgery. Mortality was defined as death within 90 days after surgery. Disease-free survival was defined as the time from surgery to diagnosis of recurrence or last follow-up visit. Overall survival was defined as the time from surgery to the date of death or last follow-up visit. Time to surgery was defined as the time between the diagnoses of hepatic metastases until liver surgery.

Matching

For a propensity matched comparison, all patients who underwent PVE before major liver resection were selected. Patients were matched with patients who had undergone major liver resection without PVE based on the variables: colon or rectal primary tumour, N stage of the primary tumour, synchronous or metachronous presentation, number of metastases, diameter of the largest metastases, neoadjuvant downsizing systemic therapy, gender and age. Patients with incomplete data of these variables were not considered for matching. Matching was performed using propensity scoring.[19] Serum CEA levels were not included as matching variable due to missing data.

Statistical analysis

Continuous variables were displayed as median with inter-quartile-range (IQR) and categorical variables by number with percentages. Continuous variables were analysed using Mann-Whitney U-tests and categorical variables using chi-square or Fisher's exact tests. Survival curves were generated according to the Kaplan-Meier method and compared using log-rank tests. Statistical analyses were performed using SPSS (version 23.0, IBM, Chicago, IL). Propensity scoring was performed using the psmatching tool for SPPS and R with the essentials for R SPSS plugin. Patients were matched 1:1 using optimal matching.

RESULTS

Between January 2000 and December 2015, a total of 1456 patients underwent a liver resection for CRLM at four high volume liver centres. Of those patients 745 underwent a major liver resection. Patient characteristics are shown in **table 1**. 53 patients (7%) underwent PVE before liver resection. Overall, PVE patients had a higher ASA classification and more often synchronous disease with more and larger metastases compared to patients who had undergone major liver resection without PVE. Although the overall incidence of postoperative complications did not differ significantly between the two groups, PVE patients experienced significantly more major complications compared to patients without PVE ($p<0.001$). Also 90-day mortality was significantly higher in patients subjected to PVE ($p=0.041$). Patients who had undergone PVE had significantly worse disease-free survival compared to patients without PVE ($p=0.017$) and a strong trend towards a worse overall survival ($p=0.052$) (**Figure 1**). The 5-year survival rate for patients who underwent a major liver resection with and without PVE was 15% and 28%, respectively.

Matched comparison

When using the variables colon or rectal primary tumour, N stage of the primary tumour, synchronous or metachronous presentation, number of metastases, diameter of the largest

Table 1. Patients and surgical characteristics

	All (n=745)	**PVE** (n=53)	**No PVE** (n=692)	*P value*
Age, *years, median (IQR)*	64 (57-71)	65 (55-69)	64 (58-71)	0.128
Male gender, *n (%)*	459 (62)	34 (64)	425 (61)	0.770
Primary tumour site, *n (%),*	*(n=741)*			0.444
- Colon	445 (60)	36 (68)	409 (59)	
- Rectum	293 (40)	17 (32)	276 (40)	
- Both	3 (0)		3 (0)	
T-stage primary, *n (%)*	*(n=700)*	*(n=47)*	*(n=653)*	0.483
- *T0*	12 (2)	-	12 (2)	
- *T1*	15 (2)	2 (4)	13 (2)	
- *T2*	112 (16)	5 (11)	107 (16)	
- *T3*	487 (70)	33 (70)	454 (70)	
- *T4*	74 (11)	7 (15)	67 (10)	
N-stage primary, *n (%)*	*(n=701)*	*(n=46)*	*(n=655)*	0.156
- N0	290 (41)	19 (41)	271 (41)	
- N1	255 (36)	11 (24)	244 (37)	
- N2	156 (22)	16 (35)	140 (22)	
Synchronous disease, *n (%) (n=729)*	414 (57)	45 (85)	369 (57)	**<0.001**
ASA classification, *n (%)*	*(n=685)*		(n=632)	**0.011**
- I	177 (26)	7 (13)	170 (27)	
- II	328 (48)	38 (72)	290 (46)	
- III	161 (24)	7 (13)	154 (24)	
- IV	18 (3)	1 (2)	17 (3)	
- V	1 (0)	-	1 (0)	
Number of metastases, *median (IQR) (n=574)*	2 (1-4)	4 (3-7)	2 (1-4)	**<0.001**
Diameter largest lesion, *mm, median (IQR) (n=569)*	45 (24-58)	50 (26-70)	36 (24-56)	**0.018**
Neoadjuvant systemic therapy, *n (%)*	410 (55)	46 (87)	364 (53)	**<0.001**
Type of resection				**<0.001**
- Multiple segments	325 (44)	5 (9)	320 (46)	
- Left hepatectomy	61 (8)	-	61 (9)	
- Extended left hepatectomy	24 (3)	-	24 (4)	
- Right hepatectomy	262 (35)	38 (71)	224 (32)	
- Extended right hepatectomy	73 (10)	10 (19)	63 (9)	
Negative resection margins, *n (%)*	600 (81)	42 (79)	558 (81)	0.869
Any complication, *n (%)*	271 (36)	27 (51)	244 (35)	0.141
Dindo grade 3-5 complication, n (%)	130 (17)	19 (36)	111 (16)	**<0.001**
90-day mortality, *n (%)*	37 (5)	6 (11)	31 (5)	**0.041**

metastases, neoadjuvant systemic therapy, gender and age, a total of 46 patients who had undergone PVE had sufficient data for matching. These patients were matched 1:1 to the 484 patients that did not undergo PVE with sufficient data for matching. The patient characteristics of the matched patient cohorts are provided in **table 2**. The groups were comparable after matching. The types of resections performed did differ between groups with predominantly right liver resections in the PVE group. There were more complications in the PVE group, and more severe complication in the PVE group. Liver failure was

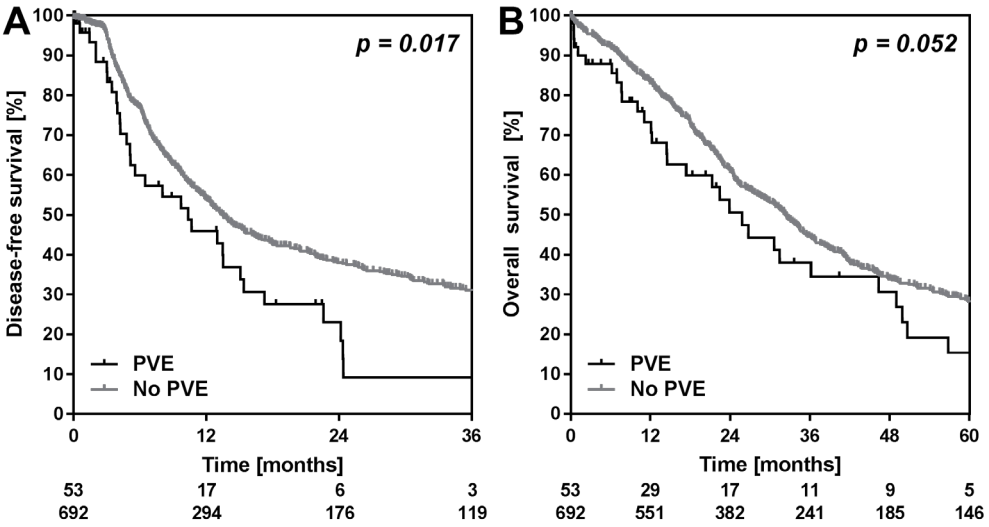

Figure 1. A: Disease free survival and **B:** overall survival in all patients who underwent major liver resection for colorectal liver metastases. Depicted below the curves are the number of patients at risk with the top number representing patients who underwent PVE and below the patients that did not undergo PVE.

uncommon in the matched groups, with only 2 occurrences in the PVE group. There was a trend towards higher 90-day mortality in the PVE groups compared to the matched controls (p=0.056). Both disease-free and overall survival were not significantly different between groups after matching (p=0.776 and p=0.537) (**Figure 2**). The 3-year DFS rates were 9% in the PVE group and 16% in the non-PVE group (p=0.776). The 5-year survival rates for patients that underwent a major liver resection with and without PVE were 14% and 14% (p = 0.866), respectively.

DISCUSSION

Patients with CRLM who undergo major liver surgery sometimes require PVE before surgery to increase the future liver remnant. There is an ongoing debate regarding the short-term safety of PVE and long-term oncological benefit. We retrospectively analysed a group of 745 patients from four liver centres in The Netherlands who underwent major liver surgery, of whom 53 underwent preoperative PVE. Patients who underwent PVE had more extensive disease in terms of number and diameter of liver metastases and more often had synchronous disease, which results in a bias towards direct comparison with non-PVE patients. After propensity score matching, PVE patients were compared to a similar cohort of non-PVE patients and had similar disease-free and overall survival.

PVE is an established technique to increase the safety of extensive liver resection by increasing volume and function of FLR, thereby reducing postoperative risk of liver

Table 2. Matched cohort of PVE and non-PVE patients

	PVE (n=46)	**No PVE** (n=46)	P value
Age, *years, median (IQR)*	65 (55-68)	62 (53-69)	0.787
Male gender, *n (%)*	29 (63)	26 (57)	0.671
ASA classification, *n (%)*			0.142
- I	7 (15)	15 (33)	
- II	32 (70)	24 (52)	
- III	6 (6)	7 (15)	
- IV	1 (2)	-	
Primary tumour site, *n (%)*			1.000
- Colon	33 (72)	32 (70)	
- Rectum	13 (28)	14 (30)	
T stage primary tumour, *n (%)*			0.078
- T0	-	3 (7)	
- T1	2 (4)	-	
- T2	5 (11)	2 (4)	
- T3	32 (70)	38 (83)	
- T4	7 (15)	3 (7)	
N stage primary tumour, *n (%)*			0.971
- N0	19 (41)	20 (44)	
- N1	11 (24)	11 (24)	
- N2	16 (35)	15 (33)	
Synchronous presentation, *n (%)*	39 (85)	39 (85)	1.000
Number of metastases, *median (IQR)*	5 (3-7)	4 (3-6)	0.900
Diameter largest tumour, *mm, median (IQR)*	5.1 (2.7-6.9)	4.4 (3.1-8.1)	0.916
Extrahepatic disease, *n (%)*	2 (4)	7 (15)	0.158
Neoadjuvant systemic therapy, *n (%)*	39 (85)	38 (83)	1.000
Type of resection, *n (%)*			**<0.001**
- Multiple segments	5 (11)	17 (37)	
- Left hepatectomy	0	4 (9)	
- Extended left hepatectomy	0	3 (7)	
- Right hepatectomy	32 (67)	12 (26)	
- Extended right hepatectomy	9 (17)	10 (22)	
Added radiofrequency ablation, *n (%)*	1 (2)	5 (11)	0.203
Negative resection margins, *n (%)*	38 (83)	35 (76)	0.607
Any complication, *n (%)*	22 (48)	11 (24)	**0.029**
Dindo grade 3-5 complication, n (%)	15 (33)	5(11)	**0.021**
90-day mortality, *n (%)*	5 (11)	-	0.056

failure.[8,9] At the same time, the potential of PVE to stimulate tumour growth remains a major concern as has been reported in several studies.[11–15] The clinical relevance of tumour progression remains a subject of debate. Progressive metastases are commonly located in the part of the liver that will be resected. These patients are thought to have a worse outcome after resection compared to patients without progression after PVE. This study shows that patients who underwent major liver resection after PVE have similar outcomes compared to patients without PVE. The relevance of tumour progression in these patients might be limited and several reports have likely been biased by the higher tumor load in

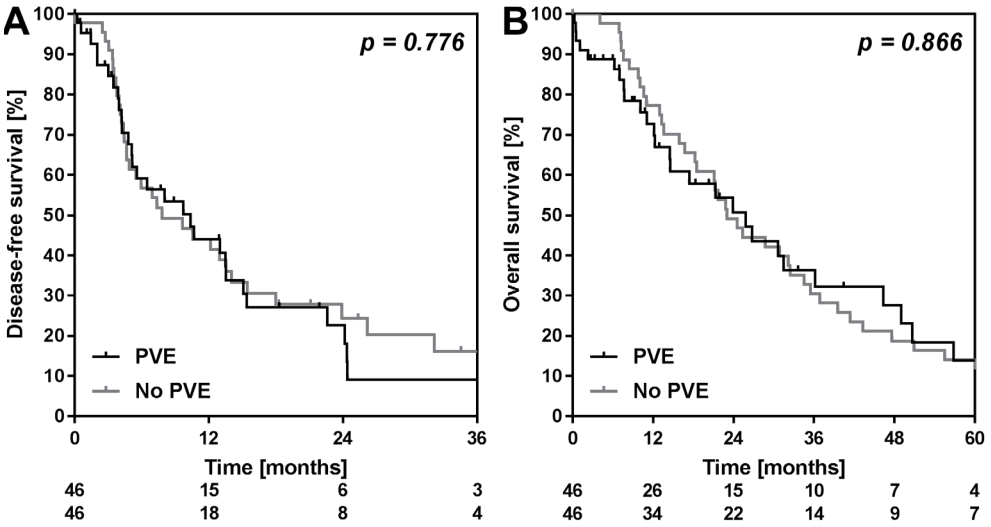

Figure 2. A: Disease free survival and **B:** overall survival in in the matched cohort. Depicted below the curves are the number of patients at risk with the top number representing patients who underwent PVE and below the patients that did not undergo PVE.

the PVE patients compared to non-PVE patients. More postoperative complications and a trend towards a higher 90-day mortality were observed in PVE patients. .[20] These impaired results may appear counterintuitive since PVE is employed to reduced postoperative complications. This study matched patients based on oncological parameters and not on surgical characteristics resulting predominantly (extended) right resections in the PVE group and more diverse procedures in the non-PVE group. This difference might account for the observed morbidity and mortality, matching analyses based on procedure characteristics might show other results.

The heterogeneity of survival outcomes among patients who had PVE and controls in the literature illustrates the complexity of the matter. Many studies reported similar survival outcomes between patients treated with or without PVE before major resection.[8,12,15,21] Wicherts et al. and Hoekstra et al. found a significantly worse overall survival in patients resected after PVE compared to non-PVE patients. Many of these studies have limitations since they had a retrospective design. In addition, comparing patients with or without PVE is difficult, since tumour burden in patients requiring PVE is usually larger and prognosis is worse. Propensity score matching probably is a better method for assessing outcomes between PVE and non-PVE patients who had undergone a major hepatectomy.

Several studies reported tumour progression post-PVE that has led to unresectable disease.[12–15] Patients who did not undergo any further surgery after PVE due to tumour progression or insufficient hypertrophy response of the FRL were excluded in our analysis. It is well known that overall survival of these patients is low.[16] The reported 5-year overall survival of 15% in the entire PVE cohort in present study could therefore be higher than all-

inclusive series on PVE patients. PVE might be considered a short-term negative oncological factor when including patients who did not proceed to resection. In the long term, PVE is most likely not a relevant oncological variable in patients once they have moved on to liver resection. 'Associating liver partition and portal vein ligation for staged hepatectomy' (ALPPS) is a new type of two-stage hepatectomy that might render some of the patients deemed unresectable after unsuccessful PVE resectable. The technique consists of two stages: 1) right portal vein ligation and in situ splitting and 2) sequential hepatectomy. ALPPS induces a more rapid hypertrophy response compared to PVE or PVL, allowing a resection within 1 or 2 weeks after the first procedure. Future studies should demonstrate whether ALPPS will provide patients a survival benefit compared to modern-day systemic therapy.[22] Furthermore it is noteworthy that all patients requiring PVE have borderline resectable or primary unresectable CRLM. Resection of CRLM provides better overall survival compared to systemic therapy for CRLM.[23] Secondary resection as therapeutic goal of systemic therapy is proven to be worth the effort.[24,25] Therefore the primary goal in systemic treatment for patients with unresectable CRLM is to downsize the metastases and convert them to resectable. In this study 89% of all PVE-patients received neo-adjuvant systemic therapy. It should also be noted the overall survival rate at 5 years was 28% in the entire cohort in the present study, which might be considered limited. However, this is likely due to the unselected, all-inclusive nature of this cohort, accounting for all treated patients including those with extrahepatic disease. Also, patients with perioperative mortality were included in the overall survival curves, which are not always considered in survival studies. The 11% of patients with perioperative mortality in both the overall and matched PVE cohort might underestimate survival in the PVE patients.

This study has several limitations. The retrospective design is a known risk for introducing selection bias. Sufficient data for matching was available in only 46 of the 53 patients who were treated with PVE and in 484 out of 692 patients who had undergone major hepatectomy without PVE was sufficient data available for matching. Notwithstanding this fact, propensity score matching is an established statistical method to limit selection bias in a heterogeneous, retrospective cohort and only patients with complete data including the parameters of the FONG score[26] were used in our analysis to ensure proper matching. The survival outcomes of this study may therefore be more reliable compared to other retrospective reports. Including patients who were not resected because of tumour progression most likely would have decreased the survival of PVE patients to below the non-PVE survival curves. Since these patients require a completely different, i.e. non-surgical treatment, we feel these patients should not be combined in a joint analysis. In addition, including patients with progression after PVE leading to unresectability would also cause selection bias, since patients with progressive disease before resection without PVE will not proceed to surgery and are not included in the dataset. Therefore, the current analyses are in our opinion most insightful. Future studies using a larger PVE cohort should aim to

compare both PVE patients who do and do not progress to surgery with patients treated with modern day systemic therapy.

In conclusion, many concerns have been raised concerning tumour progression after PVE. In this study, comparable disease free survival and overall survival were demonstrated in CLRM patients with and without PVE prior to major liver resection, indicating that tumour progression after PVE may be of trivial impact on long-term oncological outcome. Although postoperative complications were higher in patients who underwent pre-operative PVE, it remains a valuable tool to increase resectability rate of patients with CRLM.

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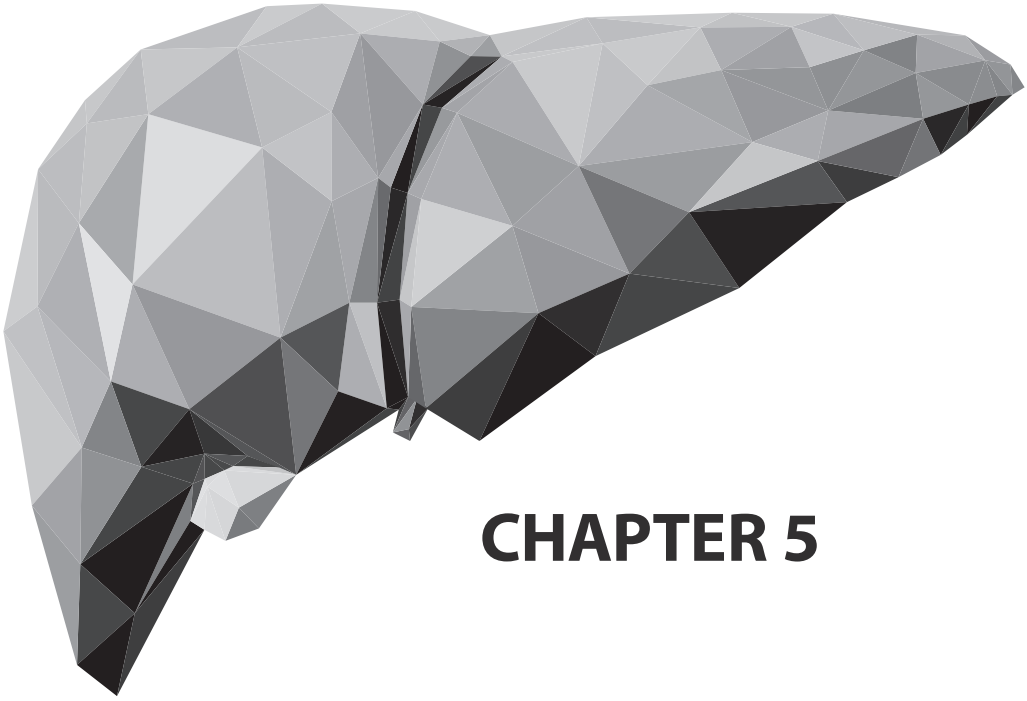

CHAPTER 5

Survival after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for advanced colorectal liver metastases: a case-matched comparison with palliative systemic therapy

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ABSTRACT

Background

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) allows the resection of colorectal liver metastases (CRLM) with curative intent which would otherwise be unresectable and only eligible for palliative systemic therapy This study aims to compare outcomes of ALPPS in patients with otherwise unresectable CRLM with matched historic controls treated with palliative systemic treatment.

Methods

All patients with CRLM from the international ALPPS registry were identified and analyzed. Survival data was compared according to the extent of disease. Otherwise unresectable ALPPS patients were defined by at least two of the following criteria: ≥6 metastasis, ≥2 future remnant liver metastasis, ≥6 involved segments excluding segment 1. These patients were matched with patients included in two phase 3 metastatic colorectal cancer trials (CAIRO and CAIRO2) using propensity scoring in order to compare survival.

Results

Of 295 patients with CRLM in the ALPPS registry, 70 patients had otherwise unresectable disease defined by the proposed criteria. Two-year OS was 49% and 72.3% for patients with ≥2 and <2 criteria, respectively ($P = 0.002$). Median DFS was 6 months compared to 12 months ($P < 0.001$) in the ≥2 and <2 criteria group respectively. Median OS was comparable between ALPPS patients with ≥2 criteria and case-matched patients who received palliative treatment (24.0 vs. 17.6 months, $P = 0.088$).

Conclusions

Early oncological outcomes of patients with advanced liver metastases undergoing ALPPS were not superior to results of matched patients receiving systemic treatment with palliative intent. Careful patient selection is essential in order to improve outcomes.

INTRODUCTION

For patients with colorectal cancer liver metastases (CRLM), liver resection is currently the only treatment with a curative intent and chance of long-term survival.[1, 2] Of all patients with CRLM, only 10-20% qualify for liver surgery mostly due to insufficient future remnant liver volume or function, or technical limitations of liver surgery.[3, 4] Staged procedures such as portal vein embolization (PVE) or ligation (PVL) followed by hepatectomy and two-stage hepatectomy have increased resectability rates by inducing future remnant liver (FRL) hypertrophy.[4] The time required between PVE and liver resection to obtain sufficient FRL hypertrophy is considered a risk for tumor progression, due to a PVE-induced growth response.[5-7] Patients with resected CRLM have 5-year overall survival (OS) rates of 35-60%.[8-10] Reported median OS in patients with unresected CRLM, however, ranges up to 18-26.7 months with modern systemic therapy and, substantial long-term survival is still unlikely.[11-13] Given the improved survival following resection, additional or improved surgical strategies that increase resectability rates could potentially improve survival in patients with CRLM.

In 2012, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced as a procedure to induce a rapid hypertrophy of the FRL.[14] The rate and speed of hypertrophy allows for more extended resections in patients with a small FRL or patients with advanced liver metastases. In the absence of consensus, ALPPS has mostly been used as alternative for two stage procedures, as well as in patients with otherwise unresectable CRLM because of advanced liver metastases. Before the availability of ALPPS, these latter patients would have been referred for palliative systemic therapy. The oncological outcomes of these patients following ALPPS are uncertain.[15-18] Other alternatives for unresectable CRLM such as systemic therapy in combination with radiofrequent ablation or selective internal radiation therapy are also emerging as alternatives.[19-21]

Therefore, we compared the outcomes of patients with CRLM treated with ALPPS who would otherwise be unresectable with other patients treated with ALPPS using ALPPS registry data. In addition, otherwise unresectable ALPPS patients were case-matched control patients who were treated with palliative systemic therapy within two prospective randomized trials in order to compare overall survival.

MATERIALS AND METHODS

ALPPS registry Patients

Ethical approval for the International ALPPS registry was obtained from the Ethics Committee Kanton Zurich in Switzerland and was registered at Clinicaltrials.gov *(Identifier: NCT01924741)*. All patients with CRLM entered in the international ALPPS registry were analyzed. The international ALPPS registry and its characteristics were described previously.[22] Briefly,

ALPPS involves portal vein ligation of the to-be resected segments, clearing the FRL of tumor, and in situ split of the liver during the first stage. The rapid hypertrophic response allows removal of the deportalized liver in the second stage when FRL volume and/or function is sufficient, usually after 1 to 2 weeks.

Patients without a reported 90-day survival status were excluded from analysis. OS and disease-free survival (DFS) for the entire cohort were with stage 1 as starting point until death or last follow-up for OS and until reported recurrence in the registry or last follow up for DFS. For the case matched comparison, OS was analyzed starting from the start of neoadjuvant systemic treatment until death of loss to follow-up, or alternatively starting at stage one. Postoperative complications were scored according to the Clavien-Dindo classification, with severe complications defined as grade IIIa or higher.[23] It should be noted the registry was primarily designed as an surgical outcome database and several oncological parameters such as extrahepatic disease and extensive chemotherapy and primary tumor data are not included in the registry.

Palliative systemic treatment cohort

Patients with unresectable liver-only metastasis were analyzed in two prospective phase 3 randomized trials conducted by the Dutch Colorectal Cancer Group (DCCG). [24, 25] The CAIRO trial randomized previously untreated and unresectable metastatic liver-only colorectal cancer metastases patients between first line-line sequential versus combination chemotherapy. CAIRO2 randomized between capecitabine, oxaliplatin, and bevacizumab, or the same regimen with the addition of cetuximab. Details of both study protocols along with results were published previously.[24, 25] Patients with at least 6 liver-only metastases were selected from these trial databases for case-matched comparison with the ALPPS patient group. Overall survival was defined as the time of randomization until the time of death or loss to follow-up.

Statistics: case-matched comparison

Main outcomes were OS and DFS. ALPPS patients were selected for analysis according to the presence of at least 2 of 3 criteria. These criteria were devised to select ALPPS patients with most advanced liver metastasis and were defined as: ≥6 metastases, ≥2 future remnant liver metastases or ≥6 involved segments excluding segment 1. These criteria were chosen as they identify a sufficient number patients for an accurate comparison, who have the most advanced liver metastases that needs extensive surgical treatment for a radical resection. The number of metastases was chosen as factor as it is a predicting factor in oncological outcomes.[6] The median number of metastases was 6, and was chosen as the cutoff. The future remnant liver metastases criterion was chosen because FLR metastases usually warrant a two-stage hepatectomy. The cut-off of two lesions was chosen, as the required metastasectomies are likely to further reduce the future remnant liver volume. The criterion

of the number of involved segments excluding segment 1 was chosen because it reflects the extent of disease as well as the required surgical treatment. The cut-off of 6 was chosen as it excludes all standard liver resections such as extended left or right liver resections. The selection based on at least two of three criteria limits the exclusion of patients with incomplete data. ALPPS patients selected using the criteria were compared to patients not selected by these criteria.

Patients of both cohorts were matched using propensity scoring[26] in order to minimize selection bias using SPSS version 22 (IBM, Chicago, IL), R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria), and the propensity score matching plugin. The used covariates were age, gender and meta-/synchronous metastases. T and N stage of the primary tumor were not available for all patients and therefore not used as matching variables, however, the T and N stages were similar between groups. Furthermore, other parameters such as WHO score were not available in the registry. Nearest-neighbor 1:1 matching was used. By using the estimated propensity score, each selected ALPPS patient was matched to a most similar control patient. Patient's characteristics were compared between both groups after matching to confirm adequate matching and ensure a most optimal comparison.

Data was presented as median with inter-quartile-range (IQR). Differences between groups were tested using Mann-Whitney U-tests for non-parametric data and using student's t-tests for continuous variables. Categorical variables were analyzed using Fischer's exact test or chi-square tests. Differences in survival curves were tested using log-rank tests. All statistical analyses were performed using SPSS version 22.0 (IBM, Chicago, IL). Propensity score matching was performed using psmatching plugin with R essentials version 2.15.2 (www.R-project.org).

RESULTS

ALPPS cohort

From the total of 608 patients submitted to the ALPPS registry, 362 patients underwent resection for CRLM between 2009 and 2015. Of these patients, 295 entered by 55 centers had sufficient follow-up data to be included in the analysis. Patient characteristics are provided in **Table 1**. Overall, stage 1 and 2 morbidity (grade ≥IIIa) was 11.1 and 28.5%, respectively, and 90-day mortality was 7.5% (**Table 2**). Mortality was 13% in center with less than 8 CRLM ALPPS cases and 4% in centers with 8 or more cases ($P < 0.01$). For the whole cohort, 2-year overall survival was 62% and 2-year DFS was 18% (**Figure 1**). The estimated median OS and DFS were 29 and 9 months, respectively.

Table 1. Main patient and operative characteristics of ALPPS patients and ALPPS patients with ≥2 or <2 criteria of unresectability

Variable	All patients (n = 295)	≥ 2 Criteria (n=70)	< 2 Criteria (n=141)	P value
Age, yr, median (IQR)	60 (53-67)	59 (50-66)	60 (54-69)	0.061
Sex, male, number, (%)	186 (64)	44 (64)	97 (69)	0.436
BMI, kg/m^2, median (IQR)	25 (23-28)	26 (23-28)	26 (23-28)	0.846
Charlson index (1-14), median (IQR)	8 (7-9)	8 (7-9)	8 (7-9)	0.709
Synchronous, number, (%)	213 (72)	65 (94)	84 (62)	0.001
T-stage primary tumor, number (%)				0.074
T1	2 (1)	1 (2)	0 (0)	
T2	13 (4)	1 (2)	9 (8)	
T3	170 (58)	48 (81)	81 (68)	
T4	51 (17)	9 (15)	29 (24)	
N-stage primary tumor, number (%)				0.004
N0	57 (19)	8 (14)	38 (32)	
N1	98 (33)	20 (36)	49 (42)	
N2	77 (26)	28 (28)	31 (26)	
CEA, ng/mL, median (IQR)	35 (8-155) *(n=190)*	42 (10-177) *(n=54)*	22 (6-125) *(n=93)*	0.262
Total metastases, number, median (IQR)	6 (3-8) *(n=170)*	9 (8-11) *(n=41)*	4 (3-6) *(n=119)*	0.001
Size largest metastasis, mm, median (IQR)	50 (34-75)	50 (32-70)	53 (35-80)	0.467
Involved segments, number, median (IQR)	5 (3-6)	7 (6-7)	4 (3-5)	0.001
Involved segments excluding segment 1		6 (6-7)	4 (3-5)	0.001
FLR metastases, number, median (IQR)	1 (0-3) *(n=214)*	4 (2-6) *(n=66)*	1 (0-1) *(n=115)*	0.001
FRLV/TLV share, %, median (IQR)	26 (19-32) (n=205)	27 (20-35) *(n=50)*	27 (20-31) *(n=107)*	0.257
Clean FLR volume, mL, median (IQR)	338 (260-441) *(n=275)*	325 (261-419) *(n=68)*	343 (266-458) *(n=134)*	0.457
Duration stage 1, min, median (IQR)	300 (240-370) *(n=267)*	320 (270-372) *(n=68)*	291 (229-360) *(n=132)*	0.011
Days between stage 1 and 2, median (IQR)	11 (8-15) *(n=282)*	11 (8-15) *(n=68)*	11 (8-15) *(n=135)*	0.982
Duration stage 2, min, median (IQR)	150 (110-200) (n=260)	150 (120-200) *(n=67)*	137 (91-195) *(n=126)*	0.156

Abbreviations: IQR, interquartile-range; BMI; body mass index, CEA; carcinoembryonic antigen, FLR; Future liver remnant, FLRV; Future liver remnant volume, TLV; total liver volume.

Selection of patients with otherwise unresectable CRLM

In order to identify patients with otherwise unresectable CRLM from the ALPPS registry, predefined criteria were devised to select these patients. In 70 of 295 patients (24%) at least two criteria were present and in 141 (48%) patients none or only one criterion was present. Eighty-four patients were excluded due to insufficient data on the presence of the criteria (**Figure 2**). Main patient and operative characteristics of both groups are provided in **Table 1** and perioperative outcomes are provided in **Table 2**. 43 of 128 patients (33%) operated

Table 2. Perioperative clinical outcomes of ALPPS patients with ≥2 or <2 criteria of unresectability

Variable	All patients (n=295)	≥ 2 Criteria (n=70)	< 2 Criteria (n=141)	P value
FRLV increase, %, median (IQR)	74 (46-100) *(n=270)*	80 (60-123)	75 (41-100)	0.036
FRLV/TLV share after stage 1, %, median (IQR)	39 (32-47) *(n=193)*	40 (33-50)	39 (32-45)	0.182
FRLV after stage 1, mL, median (IQR)	615 (481-732) *(n=271)*	632 (512-812)	623 (480-732)	0.369
R0 resection margin, n (%)	238 (92) *(n=259)*	56 (86) (n=65)	117 (94) (n=125)	0.109
Morbidity stage 1, ≥IIIa*, number (%)	31 (11)	7 (10)	17 (13)	0.652
Morbidity stage 2, ≥IIIa*, number (%)	78 (26)	16 (24)	39 (30)	0.406
90-day mortality, number (%)	22 (8)	5 (7)	10 (7)	1.000
- Centers with ≥ 8 cases	7 (4) (n=181)	1 (2) (n=43)	3 (4) (n=85)	1.000
- Centers with < 8 cases	15 (13) (n=114)	4 (15) (n=27)	7 (13) (n=56)	0.743

Abbreviations: IQR, interquartile-range; FLRV; Future liver remnant volume, TLV; total liver volume. * according to Clavien-Dindo[23]

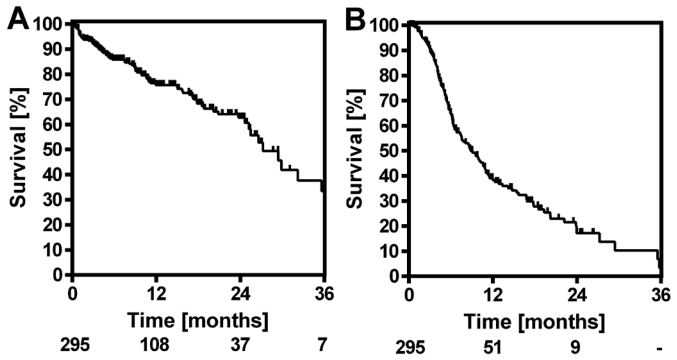

Figure 1: Survival following ALPPS for colorectal liver metastases. Overall (A) and disease-free (B) survival of patients with CRLM in the ALPPS registry. Numbers below the graph indicate the number of patients at risk at the respective time point.

in high volume centers had ≥2 criteria and 27 of 83 patients (34%) from low volume centers had ≥2 criteria (P=1.000) Although there was a trend toward lower mortality in selected and unselected patients in centers with 8 or more cases the difference did not reach statistical significance (P = 0.69 and P = 0.05, for selected and unselected patients respectively). Two-year OS was 49% in the presence of ≥ 2 criteria and 72% when <2 criteria were present while estimated median OS was 20 and 35 months, respectively (**Figure 3**, P = 0.002). Median DFS was 6 months in the presence of ≥ 2 criteria compared to 12 months for <2 criteria (**Figure 3**, P < 0.001).

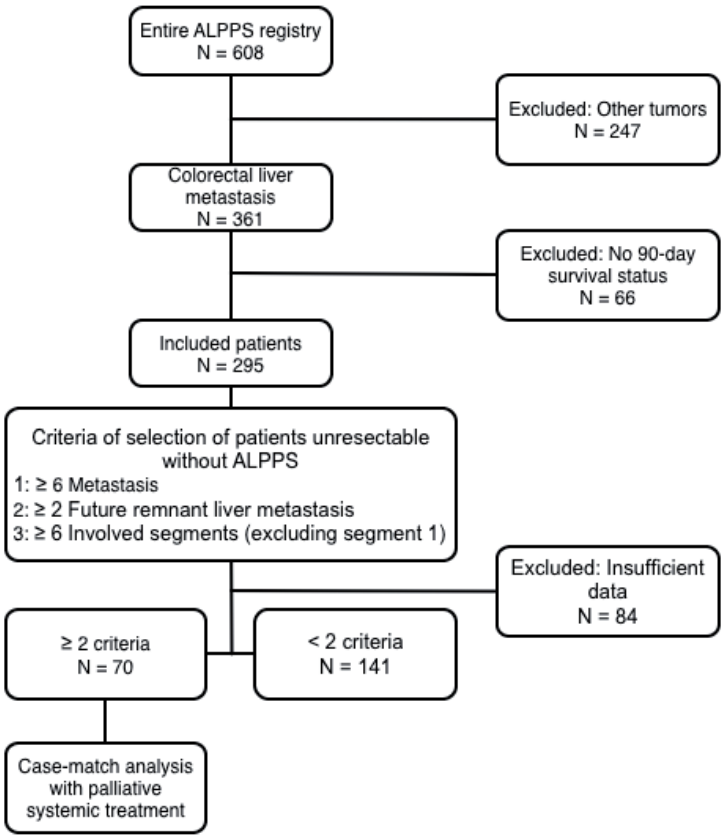

Figure 2: Patient inclusion and selection. Flow-chart illustrating the patient selection from the ALPPS registry.

A total of 60 patients had a recurrence within 6 months, 26 in the ≥ 2 criteria group and 34 in the < 2 criteria group. Of the patients with recurrence in the selected (≥2 criteria) group, 16 patients had either hepatic or extrahepatic recurrence and 10 patients had both hepatic and extrahepatic recurrence within six months after stage 1, compared to 26 and 8 patients in the unselected < 2 criteria group ($P = 0.043$)

Case-matched analysis

In order to compare the outcomes of ALPPS with palliative systemic therapy, OS of the two ALPPS groups was compared to OS of all patients from the CAIRO and CAIRO2 trial with liver-only unresected CRLM. In order to reduce selection bias, ALPPS patients with ≥2 criteria were matched (1:1) with patients who had received palliative treatment in the CAIRO 1 and 2 trials with liver only metastasis who had at least 6 metastases. Out of 481 patients with liver only metastases from CAIRO and CAIRO 2, 156 had at least 6 metastases and were eligible for (1:1) matching. Patient and disease characteristics were comparable between both

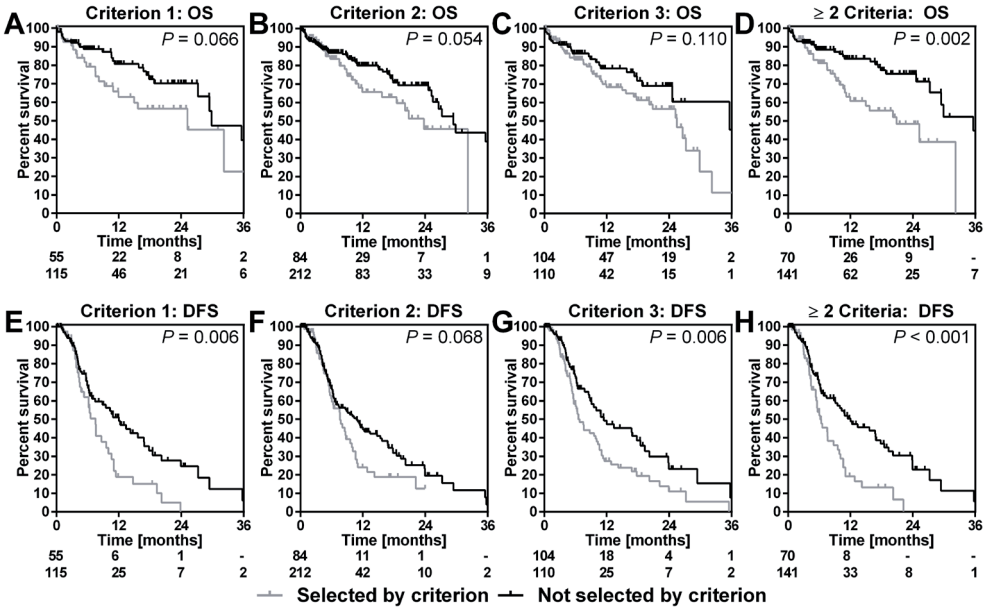

Figure 3: Extent of disease predicts overall and disease-free survival. Overall and disease-free survival of 211 ALPPS patients with CRLM according to the presence of proposed criteria for otherwise unresectable disease. Criterion 1: ≥6 metastasis, criterion 2: ≥6 involved segments excluding segment 1, and criterion 3: ≥2 FRL metastasis. Grey curves represent patients in which the respective criteria are present and black curves represent patients in which criteria are not present. Numbers below the graphs indicate the number of patients at risk at the respective time point, with the patients selected by the criteria on top, and patients not selected by the criteria below.

groups (**Table 3**). Overall survival in these matched cohorts of patients was comparable, 24.0 versus 17.6 months $P = 0.088$ (**Figure 4A**) when the start of neoadjuvant chemotherapy was considered as the starting point of survival. The median (IQR) interval between start of chemotherapy and stage one was 4 (3-6) months. Starting OS analysis at the stage one of ALPPS reduced median OS to 20 months, however this might underestimate the survival of the ALPPS patients (**Figure 4B**, $P = 0.803$).

Table 3. Case-matched analysis

	ALPPS patients with ≥ 2 Criteria (n=70)	Matched controls (n=70)	P-value
Age, yr, median (IQR)	60 (53-67)	58 (50-66)	0.644
Sex, male, number, (%)	45 (64)	50 (71)	0.469
Synchronous, number, (%)	65 (94)	66 (94)	1.000
Primary tumor resected, number (%)	41 (59)	49 (70)	0.217
T-stage primary tumor, number (%)			0.385
T1	1 (1)	-	
T2	1 (1)	3 (4)	
T3	48 (69)	28 (54)	
T4	9 (13)	6 (9)	
N-stage primary tumor, number (%)			0.578
N0	8 (11)	10 (14)	
N1	20 (29)	14 (20)	
N2	28 (40)	21 (30)	
Neoadjuvant chemotherapy, *n (%)*	68 (97)	n/a	n/a
Number of cycles, median (IQR)	7 (6-10) *(n=64)*	n/a	
CEA, ng/mL, median (IQR)	42 (10-177) *(n=54)*	42 (8-396) *(n=50)*	0.280
Total metastases, number, median (IQR)	9 (8-11)	10 (7-12)	0.227
Size largest metastasis, mm, median (IQR)	50 (32-70)	49 (31-62)	0.610

Abbreviations: IQR, interquartile-range; CEA; carcinoembryonic antigen.

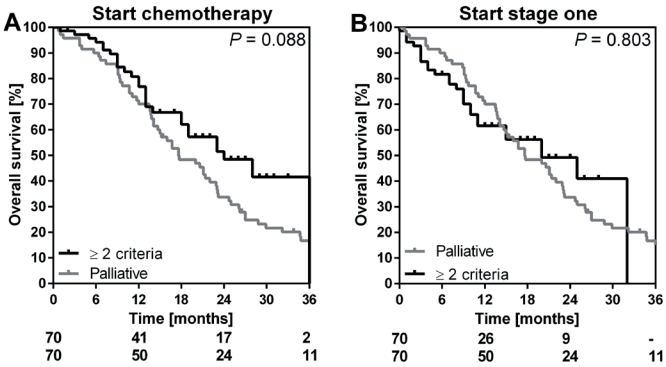

Figure 4: Survival following ALPPS for advanced colorectal liver metastasis is not superior to palliative systemic therapy. A: Overall survival of ALPPS patients with ≥ 2 criteria with analysis from the start of neoadjuvant chemotherapy compared to 70 matched controls that received palliative systemic therapy for liver-only metastases **B:** Overall survival of ALPPS patients with ≥ 2 criteria starting at stage one of ALPPS compared to 70 matched controls that received palliative systemic therapy for liver-only metastasis.

DISCUSSION

This report shows that patients with otherwise unresectable CRLM treated with ALPPS have comparable survival compared to matched controls treated with palliative systemic therapy. These patients selected according to the presence of at least two of the defined criteria have comparable postoperative morbidity and 90-day mortality compared to patients with less than two criteria. However, overall and disease free survival is inferior in the subset of patients treated with ALPPS for advanced liver metastases defined by the presence of at least 2 of the 3 devised criteria.

Median overall survival of patient with initially unresectable colorectal cancer with currently available systemic treatments is approaching 30 months in patients with mostly also extrahepatic disease.[11-13] Surgical resection of metastases offers the only chance for cure. Patients with initially unresectable disease have 1-year OS of 90-95% after liver resection following neo-adjuvant systemic therapy, with a 3-year survival of approximately 52% in these patients.[27] In the entire ALPPS CRLM cohort, 1-, and 2-year OS is 76% and 63% respectively. These differences in survival might be partially due to the initially high perioperative mortality of 12%.[14] Perioperative mortality is however decreasing and might be the result of a learning curve which was also noted after the introduction of two-stage hepatectomy.[28] The learning curve is also supported by the lower 90-day mortality in high volume centers (≥8 ALPPC CRLM cases) compared to low volume centers (<8 ALPPS CRLM cases). Also, ALPPS patients might have more extensive disease compared to patients undergoing other procedures. A better comparison for OS following ALPPS might be patients who underwent liver resection with a high clinical risk defined by a Fong score of 3 to 5. Overall survival in patients with resected CRLM with a high clinical risk score is 90% at 1 year and 70-75% at 2 years which appears superior to ALPPS.[1] Following standard two-stage hepatectomy, the reported 3-year OS is 60%.[29] Comparing these groups of patients might be troubling as the cohort of ALPPS patients is most likely very heterogeneous. Indications for ALPPS most likely vary, as ALPPS has been compared to standard hepatectomy, PVE and two-stage hepatectomy in numerous reports.[17, 30, 31] However, there is a sub-set of patients treated with ALPPS that might not have been eligible for any other surgical treatment without the ALPPS procedure. These patients are offered a new surgical perspective of which the outcomes should be examined. As resectability criteria are not uniform and vary between surgeons,[32] there are no strict criteria to select these patients. To analyze the results of ALPPS for these patients, we identified patients with advanced liver metastases from the ALPPS registry with at least two of three criteria (≥ 6 metastasis, ≥6 involved segments excluding segment 1, and ≥ 2 FRL tumors). Overall and DFS were decreased compared to ALPPS patients with <2 criteria, and remarkably, OS was not different compared to a matched palliative cohort. Although follow-up data was limited in the ALPPS patients, survival appears comparable over the first two years. Therefore, the benefit of ALPPS in

these patients is uncertain.In large series, DFS following liver resection for CRLM is 69% at 1 year and 38% at 3 years.[33] When stratified according to the Fong clinical risk score, patients with a clinical risk score of 5 have a 1-year DFS of 71% and median DFS is 22 months.[1, 34, 35] According to data collected in the ALPPS registry, 1 year DFS is 38%, In addition, 6-month DFS is 65% and median DFS is 9 months. The DFS following ALPPS is considerably lower than that reported following standard liver resection and lower than for patients with the highest clinical risk score. Following standard two-stage hepatectomy DFS is reported to be 26% at 3 years.[28] These patients might be more comparable to ALPPS patients in extent of disease with both primarily bi-lobar metastases, but the preliminary DFS data is inferior in ALPPS. These differences might be attributable to the exclusion of patients from the standard two-stage hepatectomy data who did not complete both stages of the procedure, compared to almost all patients completing both stages of the ALPPS procedure. After PVE, 20-28% of patients are not subjected to hepatic resection, mostly due to tumor progression. [17, 36] With standard two-stage hepatectomy, 31% of patients do not undergo stage two mostly due to disease progression.[29] Patients with disease progression after PVE or after the first stage of standard two-stage hepatectomy usually do not undergo any further surgery and are referred for palliative treatment. These patients would not benefit from surgery and would only be exposed to its morbidity and mortality, which might even prevent their eligibility for palliative treatment. The short interval (median 11 days) between stage one and two of ALPPS most likely does not allow sufficient time for detection of disease progression. Hence, almost all patients are subjected to both stages including its morbidity and mortality. The reduced DFS after ALPPS compared to standard two stage procedures suggests that the detection of progression has shifted from the inter-stage interval to the postoperative period following stage 2 of ALPPS. These observations were confirmed in a case matched analysis of ALPPS patients with standard two-stage hepatectomy, where DFS is lower in the ALPPS group and morbidity is higher.[30] Therefore standard two-stage hepatectomy or preoperative PVE might be preferable in terms of oncological outcomes until more data becomes available.Furthermore, in the current registry data, 55 patients did not have any FRL tumor, 25 of which had a FRL share of at least 25%. Some patients might have received ALPPS for failed PVE, the other patients could have been resected using standard hepatectomy, or standard hepatectomy with PVE. Despite the low number of patients, these patients appear to have favorable OS (1-year OS 81%) and DFS (median 16 months). In contrast, monosegmental ALPPS resections are also included in the registry.[37, 38] These patients did most likely not qualify for any other surgical resection. Considering the differences in outcomes observed in the selected subgroup of ALPPS patients in this report, it is most likely necessary to perform sub-group analysis in any ALPPS report and stratify patients according to the extent of disease. Only using these sub-group analyses, the role of ALPPS among the other treatment options of liver-only CRLM can be accurately established.

This study had several limitations. In order to compare patients who underwent

ALPPS with a palliative cohort, three criteria for selection of otherwise unresectable CRLM were devised. These criteria for selection of otherwise unresectable CRLM are subject to interpretation. Unresectability without ALPPS might differ among liver surgeons while inter-observer variability is a known factor in in the assessment of resectability in liver surgery.[32] However, definition of these criteria was necessary to be able to identify patients with advanced liver metastases in the ALPPS registry in order to assess outcomes in this sub-set of patients. Evaluation of these outcomes is essential to define the place of ALPPS in the perspective of current treatment options for CRLM. Although the retrospective data and proposed criteria are subject to bias, a clinical trial comparing ALPPS with palliative therapy is not feasible due to obvious ethical issues. Patients are voluntarily entered in the registry by collaborators and follow-up is limited, a randomized trial would provide complete and more reliable follow-up data. Also the registry is focused on perioperative outcomes, therefore oncological parameters such as chemotherapy regimens and extent of extra-hepatic disease is limited or absent.

In conclusion, ALPPS has redefined resectability and has been suggested to enhance the curative treatment potential for many patients with CRLM. However, this study shows that early oncological outcomes of patients with advanced liver metastases undergoing ALPPS, appear not better than of matched patients receiving systemic treatment. For patients with advanced CRLM and no other surgical optionthan ALPPS, the current results suggest other treatment modalities including systemic therapy might be superior. For the other patients recommendations on the indications for ALPPS remains to be established.Careful selection of patients for ALPPS and non-surgical options is advised along with adequate patient counseling, taking into account the reported increased mortality rate and uncertain oncological outcomes. Future studies should provide more definitive answers, however, randomized trials on ALPPS might be difficult in terms of methodology and inclusion. Finally, in order to better address outcomes of ALPPS, reports should include data on the extent of disease and the used indications.

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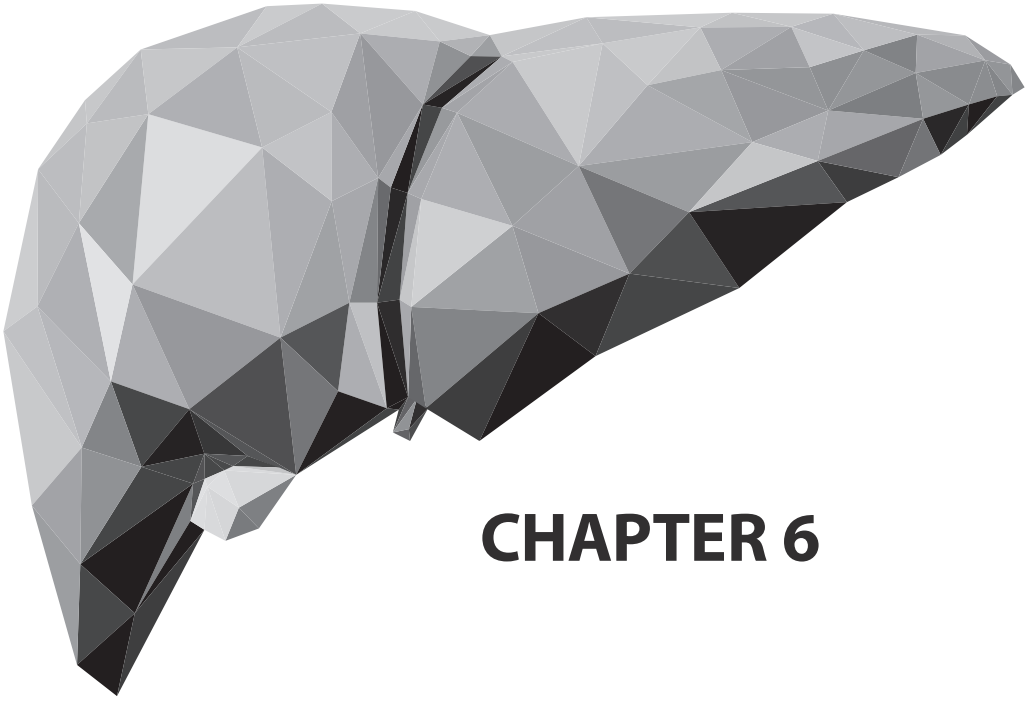

CHAPTER 6

Avoiding postoperative mortality after ALPPS – development of a tumor-specific risk score for colorectal liver metastases

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ABSTRACT

Background

ALPPS is a two-stage hepatectomy that induces more rapid liver growth compared to conventional strategies. This report aims to establish a risk-score to avoid adverse outcomes of ALPPS only for patients with colorectal liver metastases (CRLM) as primary indication for ALPPS.

Methods

All patients with CRLM included in the ALPPS registry were included. Risk score analysis was performed for 90-day mortality after ALPPS, defined as death within 90 days after either stage. Two risk scores were generated i.e. one for application before stage-1, and one for application before stage-2. Logistic regression analysis was performed to establish the risk-score.

Results

In total, 486 patients were included, of which 35 (7%) died 90 days after stage-1 or 2. In the stage-1 risk score, age ≥67 years (OR3.7), FLR/BW ratio <0.40 (OR2.9) and total center-volume (OR2.4) were included. For the stage-2 score age ≥67 years (OR 3.7), FLR/BW ratio <0.40 (OR 2.8), bilirubin 5 days after stage-1 >50μmol/L (OR2.4), and stage-1 morbidity grade IIIA or higher (OR6.3) were included.

Conclusions

The CRLM risk-score to predict mortality after ALPPS demonstrates that older patients with small remnant livers in inexperienced centers, especially after experiencing morbidity after stage-1 have adverse outcomes. The risk score may be used to restrict ALPPS to low-risk patient populations.

INTRODUCTION

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a two-stage hepatectomy, which differs from the traditional two-stage procedure in that the liver parenchyma is additionally transected partially or completely along the intended transection line during the first stage along with portal vein occlusion of the tumor-bearing segments by surgical ligation.(1) ALPPS increases and accelerates hypertrophy of the future liver remnant and reduces the time between stages from 1-2 months to 1-2 weeks when compared with conventional two-stage procedures.(2) The first ALPPS report in 2012 led to great enthusiasm about the extension of resectability, but was soon counterbalanced by the reported high morbidity and mortality.(1, 3)

The high rate of adverse events of 40% major morbidity and 12% mortality in the first report of 25 patients(1) was similar compared to the 40% major morbidity and 9% mortality rates published in the first large ALPPS registry report of 202 patients.(3) Rates of adverse events were especially high in specific subgroups, such as patients with perihilar cholangiocarcinoma with reported mortality rates up to 48%.(3-5) Indications beyond metastatic liver disease were therefore considered to be a contraindication for ALPPS at the international expert-meeting organized in order to improve safety of the procedure.(6)

In a first approach of risk stratifying, a risk score to avoid futile ALPPS was therefore created.(7) However, this risk score has limitations since it applies to all tumor entities. Since mortality is especially high in biliary tumors,(4) the events in these patients dominate the risk score and therefore, not reliably stratify the lower risk patients with CRLM. Furthermore, only cases from centers with at least five cases were included. Therefore, this study aimed to develop a risk score model to predict perioperative mortality after ALPPS in patients with CRLM as primary indication for ALPPS.

PATIENTS AND METHODS

Study Design

All patients registered in the International ALPPS Registry were eligible for inclusion in the study. The ALPPS registry is an international databases with the objective of collecting perioperative outcomes data of this novel procedure.(3) The web-based system and setup was previously described elsewhere.(3) Ethical approval for the Registry was obtained at the Cantonal Ethical Committee Zurich and the registry was registered at ClinicalTrials.gov under identifier NCT01924741. For the current analyses a registry export from November 9th 2017 was used, including all submitted cases up until the extraction date. The risk score was reported in accordance with the TRIPOD checklist.(8)

All patients who underwent ALPPS for suspected colorectal liver metastases were included. No limitations were set concerning the date of ALPPS or the date the patient was included in the registry. In addition, no limitations were set regarding total center-volume or case experience. All patients with diagnoses other than CRLM were excluded, such as patients without a reported 90-day survival status or without reported details on morbidity.

Primary and secondary outcome measures

The primary outcome was defined as mortality after stage one until 90 days after stage two. Mortality was selected as endpoint since it is not subjected to any interpretation bias. Moreover, mortality was used in the previously established futile ALPPS risk score developed in a cohort of 528 patient undergoing ALPPS for any diagnosis in centers with at least five cases.(7) Secondary outcome parameters included morbidity after stage-1 and stage-2, graded according to the classification of Dindo et al.(9) A number of patients spent in excess of 5 days in the intensive care unit, without a reported complication; in an alternative analysis these patients were classified as having a grade IVa complication.

Covariates

Covariates included patient characteristics, neoadjuvant systemic therapy, baseline volume parameters like standardized total liver volume, future liver remnant (FLR) volume, FLR to body weight (BW) ratio, standardized future liver remnant volume (sFLR) share,(10) and FLR share defined by the percentage FLR volume of true total liver volume (FLR/TLV share). These volume parameters were also calculated with data after stage-1. sFLR was calculated according to the formula: sFLR = (Future liver remnant volume/standardized total liver volume)*100%, which standardized liver volume calculated according to the method proposed by Vauthey et al.(10, 11) FLR/TLV share was calculated using the formula: FLR/TLV share = (future liver remnant volume/total liver volume)*100%. FLR/BW ratio was calculated according to Truant et al.(12) Clean FLR volume was defined as the measured FLR volume with the tumor volume subtracted. The Charlson comorbidity index was calculated with exclusion of metastatic malignancy and presence of comorbid conditions was defined , as any score above zero.

Center-volume was defined as the total number of cases entered into the database for any diagnosis. However, outcomes of the first performed cases in centers with currently high-volumes should actually be classified as low-volume center cases. Therefore the order of cases performed in each center was recorded and cases were stratified to inexperienced or experienced with a varying cut-off, this variable is termed case experience. For instance, in a center with 40 ALPPS cases, the center-volume is 40, and with a center experience cut-off at 10, the initial 9 cases in this center will be defined as inexperienced and cases 10 to 40 as experienced.

Statistical analysis

All categorical variables were displayed as number with percentages, and differences between categorical variables were analyzed using chi-square or Fisher's exact tests. Continuous variables were displayed as median with inter-quartile-range (IQR) and differences between variables were analyzed with Mann-Whitney U-tests. Missing data in the included cohort was rare and handled using full case analysis, alternatively multiple imputation was used which did not affect the risk score. Univariable analysis was performed using binary logistic regression (table S1). A risk score was generated using binary logistics regression with conditional backward selection using variables with a *P*-value below 0.10 at univariable analyses. For overlapping variables such as volume parameters and total center-volumes, a single parameter was included in the multivariable analysis. The regression coefficients were divided by the smallest factor and rounded to whole numbers in order to generate a simple risk score. Based on score points, patients were stratified into low, intermediate, and high risk groups, according to patient tertiles. Predictive performance (discrimination) of the risk score was assessed with area under the curve analysis and calibration using the Hosmer-Lemeshow test. In addition, the previously futile ALPPS risk score was calculated as previously described, and the predicted risk of futility was plotted in a graph along with the actually observed 90-day mortality risk. All statistical analyses were performed using SPSS (version 23.0, IBM, Chicago, IL) and graphs were generated using Graphpad Prism (version 7, La Jolla, CA).

RESULTS

A total of 786 cases were included in the registry at the time of data extraction for the current study, of which 498 were identified as CRLM cases and 486 had a complete 90-day follow up status (98%) and were included in the current study. The 786 procedures were performed across 139 centers with a median (range) 3 (1-66) cases per center. The included 486 cases were performed across 74 centers with a median (range) 4 (1-36) cases per center.

Baseline characteristics of the patient cohort are provided in table 1. Of the 486 who underwent stage-1 ALPPS, 35 (7%) died within 90 days after stage-1 or 2. The differences between the fatal and non-fatal cases are shown in table 1. Most notably age, FLR volume parameters and total center-volume and experience differ between these two patient groups.

The operative characteristics of stage-1, the inter-stage parameters, and outcomes of stage-2 are shown in table 2. Both stages of ALPPS were completed in 475/486 patients (98%). The most striking differences between fatal and non-fatal cases were the experienced morbidity and parameters of liver failure (i.e. plasma bilirubin and INR). Interestingly, inter-stage volume parameters did not differ between fatal and non-fatal cases .Only the

baseline liver volume parameters were predictive of outcome, and interestingly extended hepatectomy (mostly extended right hepatectomy) cases had similar outcomes compared to standard hepatectomy (mostly right hepatectomy) (table S1).

Stage-1 risk score model

In order to generate a risk score for adverse outcome, an univariable analysis was performed with baseline parameters only, in order to allow preoperative risk assessment (Table S1). The univariable analysis is shown in table S1. Using multivariable analysis and backward selection with variables with a p-value below 0.10 at univariable analysis, age over 67, baseline FLR to BW-ratio below 0.40, and total center-volume below 20 cases were identified as risk factors for mortality and included in the risk score (Table 3). The 0-to-4 risk point scale had a fair prediction with an AUC of 0.70 (0.62-0.79) at ROC curve analysis while the Hosmer-Lemeshow test showed a *P*-value of 0.63 with a chi-square of 3.5. Applying this stage-1 risk score, the low risk group (0-1 points) showed 2% mortality, the intermediate group (2-3 points) 10% mortality, and the high risk group (4 points) 21% mortality. The risk group stratification preserved the 0.70 (0.62-0.79) AUC value.

Stage-2 risk score model

In order to create a risk score for mortality after stage-2, an univariable analysis was performed for mortality including only patients who completed both stages using baseline as well as inter-stage variables (Table S2). Using variables with a *P*-value below 0.10 at univariable analysis, a multivariable analysis with backward selection was performed and identified age over 67, baseline FLR to BW-ratio below 0.40, bilirubin above 50 µmol/l 5 days after stage-1 and stage-1 morbidity of grade IIIa or higher as predictors of mortality after stage-2 (Table 4). The generated 0-to-7 point risk score showed a fair prediction with an AUC of 0.72 (0.61-0.82) at ROC curve analysis, which remained similar to 0.71 (0.61-0.81) following formation of low, intermediate, and high risk groups. Hosmer and Lemeshow testing showed a *P*-value of 0.18 with a chi-square value of 7.8. Low risk patients (0 points) experienced 1% mortality, intermediate risk (1-3 points) 6 % mortality and high risk (4-7 points) 31% mortality.

Futile ALPPS risk score(7)

Recently, a risk score was presented to predict mortality after stage-2 of ALPPS from a cohort including cases performed in centers with at least five cases and included all diagnoses.(7) Inter-stage complications of grade IIIb or higher, pre-stage-2 bilirubin and creatinine were predictive values of adverse events along with a pre stage-1 score that included tumor type and age of 67 or higher. Using an elaborate formula that included logarithmic calculation and requires a calculator, the authors generated a fair predictive model.

Figure 2 demonstrates the calculated stage-2 original futile ALPPS risk score(7) for the CRLM only cohort presented here, plotted against the predicted risk of futile ALPPS (black

Table 1. Baseline patient characteristics

	All inclusions *(n = 486)*	**Fatalities** *(n = 35)*	**Non fatalities** *(n = 451)*	**P-value**
Age, *median (IQR)*	60 (53-67)	66 (59-71)	60 (52-66)	< 0.01
≥ 67, *n (%)*	169 (35)	18 (51)	151 (34)	0.04
Male gender, *n (%)*	308 (64)	23 (66)	285 (64)	0.86
Charlston comorbidity index,				
> 0, n (%)	131 (30)	12 (39)	119 (30)	0.31
BMI, *kg/m2, median (IQR)*	25.4 (23.1-28.0)	25.4 (23.5-29.3)	25.3 (23.1-28.0)	0.37
BSA, *m2, median (IQR)*	1.88 (1.73-2.04)	1.87 (1.69-2.07)	1.88 (1.73-2.04)	0.95
sTLV, *mL, median (IQR)*	1588 (1395-1791)	1575 (1347-1829)	1588 (1398-1791)	0.93
Number of lesions, *median (IQR)*	6 (4-10)	7 (2-11)	6 (4-10)	1.00
Largest Metastasis, *mm,*				
median (IQR)	49 (31-73)	46 (30-65)	49 (31-75)	0.65
Neoadjuvant therapy, *n (%)*	434 (89)	30 (89)	404 (89)	0.77
Over 6 months neoadjuvant				
therapy, *n (%)*	86 (19)	4 (13)	82 (2)	0.83
Previous liver surgery, *n (%)*	46 (10)	3 (9)	43 (10)	1.00
Previous PVE, *n (%)*	18 (4)	2 (6)	16 (4)	0.36
FLR volume clean, *median (IQR)*	341 (260-432)	315 (246-375)	346 (261-441)	0.12
				0.05
FLR/TLV share, *%, median (IQR)*	26 (20-32)	24 (19-36)	26 (20-32)	0.86
FLR/BW ratio, *median (IQR)*	0.34 (0.26-0.43)	0.32 (0.25-0.37)	0.35 (0.26-0.44)	0.12
< 0.40	293 (66)	28 (85)	265 (64)	0.02
sFLR share, *% median (IQR)*	22 (17-27)	20 (16-25)	22 (17-28)	0.11
< 20 %, *n (%)*	184 (41)	19 (58)	165 (40)	0.07
Open approach, n (%)	455 (94)	33 (94)	422 (94)	0.98
Extended hepatectomy, n (%)	263 (54)	21 (64)	242 (56)	0.47
Total center-volume, *n (%)*				
< 20 cases	220 (45)	22 (63)	198 (44)	0.04
Case experience, *n (%)*				
< 8 cases	236 (49)	22 (63)	214 (48)	0.08
CRLM case volume, n (%)				
< 8 cases	186 (38)	17 (49)	169 (38)	0.21

dots). The red dots represent the observed mortality rates according to the corresponding risk scores. However, since almost all CRLM patients are low risk in the original score, the red dots in the highest risk scores only represent a handful of patients. Therefore the CRLM cohort was stratified to eight proportional cohorts with the respective observed mortality according to the median risk original all-tumor-entity futile score in the group. As demonstrated by the green dots almost all CRLM cases are in the lower part of the risk stratification, as was expected. Therefore the risk score does not adequately stratify CRLM patients.

Table 2. Operative characteristics and outcomes

	All inclusions *(n = 486)*	**Fatalities** *(n = 35)*	**Non fatalities** *(n = 451)*	***P*-value**
Stage-1 duration, *min, median (IQR)*	300 (240-372)	315 (270-420)	300 (240-370)	0.22
Transfusion stage-1, *any, n (%)*	100 (21)	8 (23)	92 (20)	0.32
Morbidity stage-1, *n (%)*				
- Any	140 (29)	17 (49)	123 (27)	0.01
- Grade IIIa or higher	52 (11)	13 (37)	39 (9)	< 0.01
- Grade IVa or higher	16 (3)	8 (23)	8 (2)	< 0.01
- Grade IVa or higher, or > 5 days ICU stay	61 (13)	13 (37)	48 (11)	< 0.01
Completed both stages, *n (%)*	475 (98)	33 (94)	442 (98)	0.18
Bilirubin POD day 5, *µmol/L, n (%)*	13 (9-23)	21 (12-110)	12 (9-21)	< 0.01
INR POD day 5, *median (IQR)*	1.1 (1.0-1.2)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	0.02
Inter-stage FLR volume clean, median (IQR)	600 (487-720)	606 (483-714)	600 (487-723)	0.63
Inter-stage FLR/TLV share, *%, median (IQR)*	38 (32-46)	39 (31-47)	38 (32-46)	0.78
Inter-stage FLR/BW ratio, *median (IQR)*	0.60 (0.49-0.72)	0.61 (0.48-0.72)	0.60 (0.49-0.72)	0.66
Inter-stage sFLR share, *% median (IQR)*	36 (29-45)	32 (25-44)	36 (29-45)	0.13
FLR volume increase, *%, median (IQR)*	71 (49-100)	65 (26-97)	72 (41-100)	0.29
Bilirubin before stage-2, *µmol/L, median (IQR)*	13 (8-24)	26 (11-44)	12 (8-22)	< 0.01
INR before stage-2, *median (IQR)*	1.1 (1.0-1.2)	1.2 (1.1-1.4)	1.1 (1.0-1.2)	0.04
Duration stage-2, *min, median (IQR)*	150 (110-210)	187 (137-229)	150 (110-201)	0.03
Transfusion stage-2, *any, n (%)*	95 (20)	16 (49)	79 (18)	< 0.01
Morbidity stage-2, *n (%)*				
- Any	266 (56)	33 (100)	235 (53)	< 0.01
- Grade IIIa or higher	152 (32)	33 (100)	119 (27)	< 0.01
- Grade IVa or higher	49 (10) 89 (19)	33 (100)	16 (4)	< 0.01
- Grade IVa or higher, or > 5 days ICU stay		33 (100)	56 (13)	<0.01
Morbidity any stage, *n (%)*				
- Any	322 (66)	35 (100)	287 (64)	< 0.01
- Grade IIIa or higher	187 (39))	35 (100)	152 (34)	< 0.01
- Grade IIIb or higher	61 (13)			
- Grade IVa or higher		35 (100)	28 (6)	< 0.01
Grade IVa or higher, or > 5 days ICU stay	123 (25)	35 (100)	90 (20)	< 0.01

Table 3. Multivariable analysis for mortality – stage-1 risk score

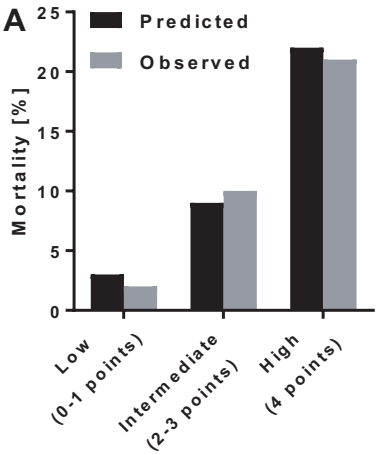
	Odds ratio (95% CI)	*P*-value	Risk score points
Age > 67 years	3.0 (1.4-6.2)	0.04	2
FLR to BW ratio < 0.40	2.9 (1.1-7.7)	<0.01	1
Total center-volume < 20 cases	2.0 (0.9-4.2)	0.08	1

Table 4. Multivariable analysis for mortality – stage-2 risk score

	Odds ratio (95% CI)	*P*-value	Risk score points
Age > 67 years	3.7 (1.6-8.2)	< 0.01	2
FLR to BW ratio < 0.40	2.8 (1.0-7.9)	0.05	1
Bilirubin > 50 µmol/L POD 5 of stage-1	2.4 (1.0-5.9)	0.05	1
Stage-1 morbidity grade IIIa or higher	6.3 (2.5-15.9)	< 0.01	3

Stage one risk score

Age ≤ 67 years	2 points
Baseline FLR to BW ratio < 0.40	1 point
Center volume < 20 cases	1 point



Stage two risk score

Age ≤ 67 years	2 points
Baseline FLR to BW ratio <0.40	1 point
Bilirubin ≥ 50 µmol/L POD 5	1 point
Stage one morbidity ≤ grade IIIa	3 points

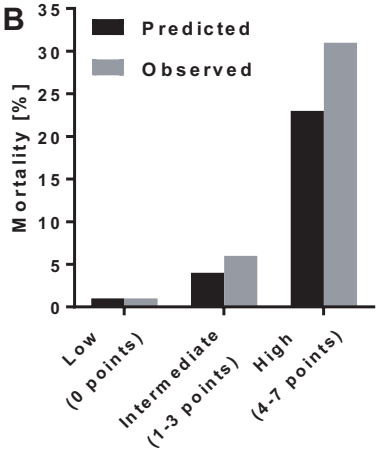


Figure 1. (A) Stage-1 risk score parameters and weight. The predicted and observed mortality stratified according to the risk groups based on the stage-1 risk scores. **(B)** Stage-2 risk score parameters and weight. The predicted and observed mortality according to the risk groups bases on the stage-2 risk scores.

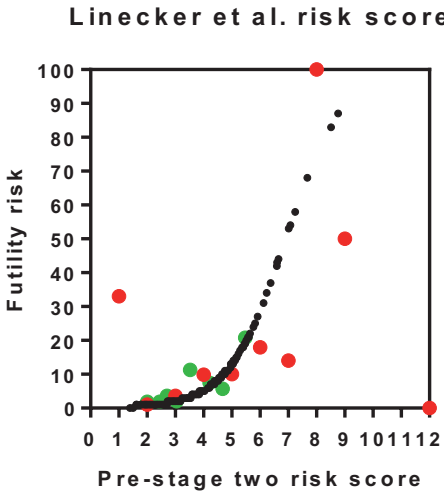


Figure 2. The Futile ALPPS risk score as proposed by Linecker et al.(7) plotted against the predicted risk of futile ALPPS in black dots. The red dots represent the observed mortality rates according to the corresponding risk scores rounded to whole numbers. The green dots represent the entire cohort stratified in eight proportional groups based on the Linecker et al risk score, with the median group score plotted against the observed mortality.

DISCUSSION

In this study the concept of risk assessment in ALPPS was revisited based on two premises. First, only CRLM were included since biliary tumors were felt to be contraindications to ALPPS. Second, two separate risk scores were generated in order to predict the risk of mortality following stage-1 or 2 of ALPPS using variables available before the respective stage in order to allow risk assessment. Both risk scores achieved fair predictive value with AUC values above 0.70, and allow adequate stratification of CRLM patients into low, intermediate, and high risk subgroups.

ALPPS has generated both enthusiasm as well as criticism since its introduction in 2012. It induces an accelerated increase in liver volume compared to conventional two-stage procedures, thereby reducing the time interval between stages and increasing the proportion of patients who undergo complete resection from 57-72% to 92-98%.(3, 13-15) This results in a potential increase in resectability; however, at the price of increased mortality and also uncertainty regarding the oncological outcomes. Disease progression that most frequently is the reason for cancellation of the second stage in conventional procedures will not be detected in ALPPS because of the short inter-stage interval.(15) Therefore, the detection of progressive disease will most likely have shifted to the postoperative period, accounting for the low disease-free survival reported before.(15) Whether the increase in resectability using ALPPS outweighs the expected higher recurrence rates remains to be

established. An additional factor that puts oncological outcomes at risk, is the fact that disease that was conventionally considered unresectable, may be rendered resectable using the ALPPS technique.(15, 16)

The current analyses showed that a considerable proportion of patients (11%) with CRLM undergo ALPPS without neoadjuvant chemotherapy. This practice may lead to suboptimal oncological outcomes since the patients in which ALPPS should be considered are patient with initially non-resectable liver metastases and would therefore be eligible for systemic therapy in the context of a conversion strategy.(17)

Considering these oncological uncertainties, the potential benefits of ALPPS over conventional techniques of regenerative liver surgery become only visible if the perioperative outcomes are not at least comparable to these techniques. In the initial reports of ALPPS, mortality was high with reported rates of 9-12% and grade IIIa morbidity or higher occurring in 40% of patients.(1, 17) A more recent registry report demonstrates a reduction of mortality in the most recent years below 5% and of major morbidity to round 10%, comparable with conventional major liver resection.(18) However, this report only included patients from centers with at least 10 cases over a three-year period, thereby excluding 399 of a total of 836 cases from the analysis while accepting that ALPPS is performed for all indications. Outcomes are likely improving in high volume centers due to patient selection. However, the inclusion of all tumor types results in heterogeneous cohorts, with results that are difficult to interpret. Furthermore, the exclusion of low volume centers from analyses hampers the generalization and application of results to all centers performing ALPPS.

The "futile ALPPS risk score" reported before intends to guide the decision to progress to stage-2 of ALPPS.(7) However, this score included only patients from centers with at least 5 cases, thereby 83 patients from the analysis. Biliary tumors have mortality up to 48%(4) and therefore biliary tumor type obviously dominates the "futile ALPPS risk score". CRLM is the most common and possibly only indication for ALPPS and overall have a lower risk. There patients are not stratified well with this score as shown in **Figure 2** and the majority of CRLM are in the low risk region of the score, which does not allow adequate risk stratification of these patients. A CRLM specific risk score might perform better in risk assessment and aid clinical decision making in this group of patients. In addition, the "futile ALPPS risk score" is somewhat complicated and requires calculators to perform the log-calculation of the scores.

The current risk score includes only CRLM patients and did not exclude any patient based on total center-volume but rather used total center-volume and experience as variables in the analyses. The current data indeed show that total center-volume is a predictor of outcomes, along with age above 67 years and a small FLR volume to BW ratio. The predictive value of baseline FLR volume for mortality in both risk scores suggests volume augmentation with PVE before ALPPS could further improve outcomes and suggests PVE should be considered first before proceeding to ALPPS. The predictive value of stage-1 morbidity for

adverse outcomes after stage-2 was reported before,(7, 19) and suggests stage-2 should not be rushed in these patients. The predictive value of high bilirubin levels 5 days after stage-1 points to the dominant reason for morbidity, post-hepatectomy liver failure(20) and again suggests stage-2 should be postponed in these patients until complete recovery, for instance with complete normalization of bilirubin levels.

Interestingly, none of the inter-stage FLR volume parameters were predictors of adverse outcomes following stage-2 of ALPPS. This observation is remarkable, since baseline FLR volumes are low in ALPPS and an increased hypertrophic response would suggest a good outcome, which as shown not to be the case in this study. The lack of predictive value seems to confirm that the volumetric increase of the FRL in ALPPS is not accompanied by a proportional increase in function of the FRL,(21) something that has been shown to be the case in PVE.(22)

This study has several limitations, first of all the retrospective nature and voluntary basis of data collection in the registry, which does not guarantee inclusion of all cases performed in participating centers, creating a reporting bias. Also, many data points in the registry are incomplete, such as the used modifications of ALPPS. The modified ALPPS procedures applied in all centers together with distinct protocols for assessment and different treatment preferences were all included, unevitably resulting in a heterogeneous cohort. However, the current report is the largest, detailed ALPPS cohort about CRLM undergoing ALPPS. A second limitation is that the number of events (90-day mortalities) is small and limits the power of this study. Alternative risk scores for grade IVa or higher morbidity were considered to increase the power, however, it was noticed that while 61 patients experienced a grade IVa or higher complication following either stage of ALPPS, a further 62 patients did not have a grade IVa reported complication but did spend longer than 5 days in the ICU following either stages. It is unlikely that these patients spent these ICU days merely for observation and a complication requiring ICU treatment seems likely in these patients. Since mortality is a straightforward, endpoint that is difficult to manipulate by reporting, it was chosen as primary endpoint. At last, the score presented in this study has only undergone internal validation, and external validation should be undertaken in future studies in different cohorts. However, interval discrimination was good as demonstrated by the AUC values (0.70 (0.62-0.79) and 0.72 (0.61-0.82)) and the score showed good calibration as demonstrated by the Hosmer-Lemeshow tests (3.5 with $P = 0.63$ and 7.9 with $P = 0.18$) of both scores.

Patient selection is essential to improve the outcomes of ALPPS. The score presented assists clinical decision making and guide treatment in patients with CRLM who are considered for ALPPS. The analyses suggests patients with unilateral metastases should undergo PVE followed by resection since baseline liver volume is predictive of outcome, and only proceed to ALPPS in the case of insufficient liver hypertrophy. For older patients and those with a liver to body-weight-ratio of > 0,4 a first attempt at conventional two-stage

hepatectomy with PVE may well be preferable, and for inexperienced teams a referral to a more experienced center should be considered. In patient with profound liver dysfunction after stage 1, caution is warranted in proceeding to a stage-2 and some might have better outcomes with conversion to a palliative treatment paradigm. For this analysis a homogenous cohort consisting only of CRLM patient even from centers with the experience of less than 5 patient represents a more realistic scenario to contribute to pragmatic improvement in patient selection. Using this risk score CRLM patients can be stratified to low, intermediate, or high risk, where the majority of patients would be stratified as low risk in the original futile ALPPS risk score.

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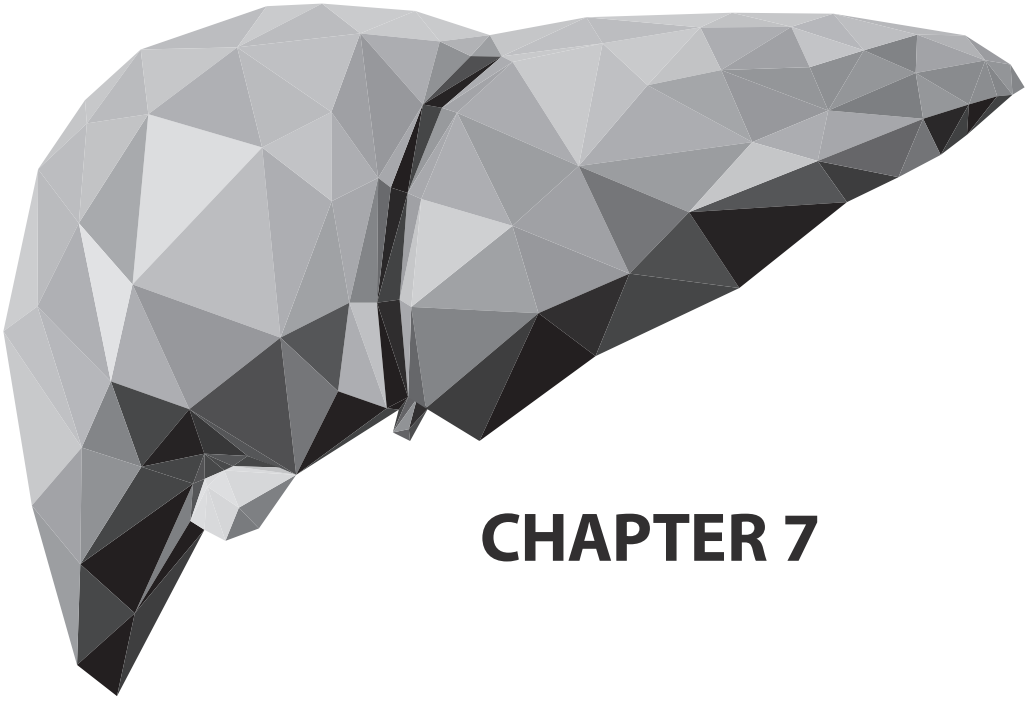

CHAPTER 7

Hepatic vascular inflow occlusion is associated with reduced disease free survival following resection of colorectal liver metastases

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ABSTRACT

Background

Hepatic vascular inflow occlusion (VIO) can be applied during resection of colorectal liver metastases (CRLM) to control intra-operative blood loss, but has been linked to accelerated growth of micrometastases in experimental models. This study aimed to investigate the effects of hepatic VIO on disease-free and overall survival (DFS and OS) in patients following resection for CRLM.

Methods

All patients who underwent liver resection for CRLM between January 2006 and September 2015 at our center were analyzed. Hepatic VIO was performed if deemed indicated by the operating surgeon and severe ischemia was defined as ≥ 20 minutes continuous or ≥ 45 minutes cumulative intermittent VIO. Cox regression analysis was performed to identify predictive factors for DFS and OS.

Results

A total of 208 patients underwent liver resection for CRLM. VIO was performed in 64 procedures (31%), and fulfilled the definition of severe ischemia in 40 patients. Patients with severe ischemia had inferior DFS (5-year DFS 32% vs. 11%, $P < 0.01$), and inferior OS (5-year OS 37% vs. 64%, $P < 0.01$). At multivariate analysis, a high clinical risk score (Hazard ratio (HR) 1.60 (1.08-2.36)) and severe ischemia (HR 1.89 (1.21-2.97)) were independent predictors of worse DFS. Severe ischemia was not an independent predictor of OS.

Conclusion

The present cohort study suggests that prolonged hepatic VIO during liver resection for CRLM was associated with reduced DFS. A patient-tailored approach seems advisable although larger studies should confirm these findings.

INTRODUCTION

Surgical indications for resection of CRLM have been extended during the last decades.[1] Limitations regarding number, size and localization of CRLM have been replaced by one main criterion, namely sufficient future remnant liver volume and function.[2] Surgery for CRLM has increasingly become part of a multimodality approach, including downstaging systemic therapy, local ablation modalities and treatment of limited extrahepatic metastases.[1,3]
The extended indications and extended resections within a multimodality approach have increased the risks of postoperative morbidity.[4] Intra-operative blood loss has mainly been associated with compromised clinical outcomes[5] and reduced survival[6], and therefore, vascular inflow occlusion (VIO, or Pringle maneuver) is frequently used during parenchymal transection to reduce blood loss [7,8] VIO, however, inevitably leads to temporary ischemia of the liver parenchyma. Although most livers can tolerate up to 120 min of (intermittent) ischemia, subsequent reperfusion induces hepatic ischemia/reperfusion (IR) injury of which the impact is correlated with the duration of ischemia .[9]

Hepatic IR is characterized by the formation of reactive oxygen species and inflammation causing hepatocellular necrosis, which can compromise postoperative function of the liver remnant.[10] Furthermore, hepatic IR has been shown to accelerate outgrowth of hepatic colorectal micro-metastasis up to 6-fold in animal models.[11-13] The clinical oncological impact of hepatic IR is still subject of debate. A recent systematic review reported no influence of VIO on overall survival (OS) following resection of CRLM.[14] The impact of VIO on disease free survival (DFS) is less well established with contradictory findings in literature.[15,16] While some confirmed the preclinical finding of increased recurrence with application of VIO,[16] others found a protective effect of VIO on recurrence.[15] This study aimed to investigate the effects of hepatic VIO during resection of CRLM on DFS and OS.

METHODS

Patients
All consecutive patients who underwent liver resection with curative intent for CRLM between January 2006 and September 2015 at the Academic Medical Center, Amsterdam, the Netherlands, were included. Data were retrospectively collected from prospective data registrations.

Preoperative evaluation
Standard preoperative work-up included computed tomography (CT) of the abdomen and chest as well as measurement of plasma carcinoembryonic antigen (CEA) levels along with other routine blood tests. Magnetic resonance imaging (MRI) of the liver and positron

emission tomography (PET) were selectively performed. All patients were discussed in a multidisciplinary meeting including surgeons, medical oncologists and radiologists.

Major liver resection was defined as resection of at least 3 Couinaud liver segments.[17] In the case of suspected major liver resection, future remnant liver (FRL) volume was routinely assessed by CT-volumetry, along with FRL function using ^{99m}Tc-mebrofenin hepatobiliary scintigraphy.[2] When considered insufficient (FRL volume < 25% and/or HBS < 2.7 %/min/m^2), portal vein embolization was performed prior to resection.

Surgery

Abdominal exploration and liver ultrasonography were performed in all cases to confirm tumor resectability and to evaluate the presence of extrahepatic disease. Parenchymal dissection of the liver was routinely done using the ultrasonic dissector (Cavitron Ultrasonic Aspirator, Valleylab, Boulder, CO, USA) and bipolar forceps. Minor liver resections and metastasectomies were performed laparoscopically since 2011 when considered feasible. Major liver resections were selectively performed using a laparoscopic approach since 2014; currently only as part of an ongoing randomized clinical trial comparing open and laparoscopic hemihepatectomy (clinicaltrials.gov identifier NCT01441856). Hepatic VIO was performed when deemed indicated by the operating surgeon in order to reduce intra-operative blood loss. Intermittent VIO using cycles of 20 minutes ischemia followed by 10 minutes of reperfusion was the preferred regimen.

Follow-up included hepatic ultrasonography or abdominal CT with imaging of the thorax (plane X-ray or CT) every 3 to 6 months during the first 2 years and every 6-12 months thereafter. CEA was measured every 3 to 6 months. Adjuvant chemotherapy is not part of standard treatment protocols and guidelines in the Netherlands, due to the absence of a benefit in OS.[18]

Study variables

Study variables included patient characteristics, CEA level before resection, primary tumor T and N stage, number of hepatic lesions, size of the largest lesion, synchronous or metachronous presentation of metastases and operative details. Severe ischemia was defined as ≥ 20 minutes continuous or ≥ 45 minutes cumulative intermittent ischemia, according to a previous report.[16] Considering that VIO is liberally applied even when blood loss is limited, severe ischemia was chosen as study variable and lesser durations of ischemia were defined as mild. Primary outcome parameters were DFS, defined as the time from liver resection until first recurrence or loss to follow-up, and OS, defined as the time between surgery for hepatic metastasis and death or loss to follow-up. Secondary outcome parameters included morbidity according to Clavien-Dindo classification, with at least grade IIIa defined as major complications[19], mortality defined as death within 90 days after surgery, and intrahepatic recurrence. Survival was obtained via the national municipal personal records database.

Statistical analysis

DFS and OS were analyzed and visualized using Kaplan-Meier analysis. Differences in actuarial survival probabilities between relevant subgroups were analyzed using log-rank tests. Multivariate analysis of predictive factors for DFS and OS was performed using cox regression and repeated for hepatic recurrence only. Variables with a P-value below 0.20 at univariate analysis were included in the model, with backward selection. The clinical risk score according to Fong[20] was used for the purpose of multivariate analysis of prognostic factors instead of the separate criteria. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 22.0 (IBM, Chicago, IL).

RESULTS

Patients

A total of 208 patients underwent liver resection for CRLM between January 2006 and September 2015. Baseline characteristics are shown in table 1. Primary tumor characteristics were not available in three patients, because of resection of the primary tumor at a referring hospital or death before resection of the primary tumor in patients with a liver-first strategy.

Operative data

Operative data and outcomes are provided in table 2. Of the 208 procedures, 81 (39%) were major hepatectomies. Forty procedures (19%) were performed laparoscopically, of which 6 major resections. VIO was more often applied during major liver resection compared to minor liver resection (48% vs 29%, P < 0.001). Forty patients (19%) were subjected to at least 20 minutes continuous or 45 minutes intermittent hepatic ischemia (defined as severe ischemia). Seventy-four patients (36%) experienced at least one complication, and severe complications occurred in 54 (26%) patients with a Clavien-Dindo grade IIIa or higher. Two patients died within 90-days after surgery (1%).

Disease-free survival

Median follow-up was 35 months. In the entire cohort, DFS at 1, 3, and 5 years was 59%, 36%, and 29% respectively. Patients subjected to severe ischemia had inferior DFS compared to patients operated with mild, or, without severe ischemia (Figure 1B, 5-year DFS 32% vs. 28% vs. 11%, P < 0.01). Predictors of DFS are shown in table 3. Portal vein embolization (HR 1.78 (1.03-3.09), P = 0.04), >3 hepatic lesions (HR 1.66 (1.06-2.58), P < 0.01), and a high clinical risk score according to Fong[20] (1.64 (1.11-2.42), P < 0.01), and severe ischemia (HR 1.93 (1.23-3.02), P < 0.01) influenced DFS at univariate analysis. At multivariate analysis, a high clinical risk score (HR 1.60 (1.08-2.36), P = 0.02) and exposure to severe ischemia (HR 1.89 (1.21-2.97),

Table 1. Baseline characteristics

	N=208
Age, *years, median (IQR)*	64 (56-71)
Male, *n (%)*	136 (65)
BMI, *kg/m^2, median (IQR)*	24.9 (22.7-27.9)
Portal vein embolization, *n (%)*	22 (11)
Number of lesions, *median (IQR)*	2 (1-3)
Largest lesion, *mm, median (IQR)*	31 (20-51)
CEA level, *ng/dL, median (IQR)*	7 (3-33)
Synchronous liver metastasis, *n (%)*	141 (68)
Preoperative chemotherapy, *n (%)*	154 (74)
Preoperative targeted therapy, *n (%)*	54 (26)
Location primary tumor, *n (%)*	
Colon	113 (54)
Rectum	92 (44)
T-stage primary tumor, *n (%)*	
T0	1 (1)
T1	8 (4)
T2	44 (21)
T3	132 (64)
T4	20 (10)
N stage primary tumor, *n (%)*	
N0	87 (42)
N1	78 (37)
N2	40 (19)
Fong clinical risk score, *n (%)*	
0-2, low risk	137 (66)
3-5 high risk	71 (34)

P < 0.01) were identified as independent predictors of DFS. Univariate analysis for hepatic recurrence with a P value below 0.2 were severe ischemia (mild ischemia (HR 0.85 (0.26-2.78), P = 0.78 and severe ischemia HR 2.50 (1.29-2.85), P < 0.01), PVE (HR 1.19 (0.96-3.07), P = 0.07), high clinical risk score (HR 2.69 (1.49-4.87), P < 0.01), intraoperative transfusion (HR 1.62 (0.84-3.16), P = 0.15), and preoperative systemic therapy (chemotherapy HR 2.19 (0.92-5.19). Multivariate analysis for hepatic disease recurrence revealed similar results with severe ischemia (mild ischemia HR 0.83 (0.27-2.88), P = 0.87, severe ischemia HR 2.41 (1.24-4.69), P <0.01) and a high clinical risk score (hazard ratio 2.65 (1.46-4.81), P < 0.01) as independent predictors of hepatic disease recurrence.

Overall survival

In the entire cohort, OS at 1, 3, and 5 years was 94%, 76%, and 59%, respectively (Figure 1A). OS was also inferior in patients subjected to severe ischemia compared to mild or no ischemia (Figure 1C, 5-year OS 64% vs. 63% vs. 37% vs. 64%, P = 0.04). Predictors of OS in table 3. Besides severe ischemia (HR 2.12 (1.18-3.80), P = 0.01), portal vein embolization

Table 2. Operative data and outcomes

	N=208
Procedure performed, *n (%)*	
Right hepatectomy	47 (23)
Extended right hepatectomy	12 (6)
Left hepatectomy	14 (7)
Extended left hepatectomy	2 (1)
Segmentectomy	60 (29)
Local resection	73 (35)
Major hepatectomy, *n (%)*	81 (39)
Laparoscopic procedure, *n (%)*	40 (19)
Simultaneous primary tumor resection, *n (%)*	28 (14)
Pringle maneuver, *n (%)*	
Not performed	144 (69)
Intermittent	29 (14)
Continuous	35 (17)
Total pringle maneuver duration, *min, median (range)*	60 (10-120)
Ischemia, n (%)	
Mild	23 (11)
Severe	40 (19)
R0 resection margin, *n (%)*	171 (82)
Hospital stay, *days, median (IQR)*	7 (5-11)
Morbidity, *n (%)*	
Any complication	74 (36)
Clavien-Dindo grade IIIa or higher	54 (26)
ICU stay, *n (%)*	20 (10)
90-day mortality, *n (%)*	2 (1)

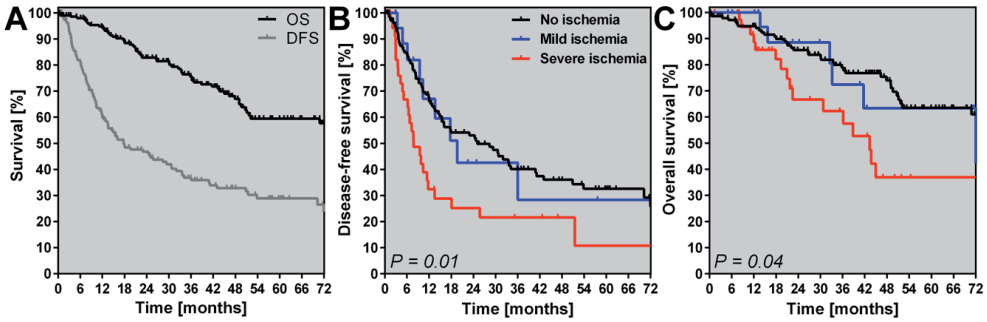

Figure 1: A: DFS and OS of 208 patients who underwent liver resection for CRLM. B: Comparison of DFS in 40 patients operated with severe ischemia to 23 with mild ischemia and, 145 patients operated withoutischemia. C: Comparison of OS in 40 patients operated with severe ischemia to 23 with mild ischemia, and with 145 patients operated without ischemia. Differences in survival curves were analyzed using log-rank tests. Abbreviations: OS, overall survival; DFS disease-free survival.

(HR 2.52 (1.34-4.78), P < 0.01), a CEA level over 200 ng/mL (HR 2.90 (1.31-6.43), P < 0.01), non-radical resection (HR 2.13 (1.21-3.77), P < 0.01), and intraoperative red blood cell transfusion (2.15 (1.28-3.63), P < 0.01) also influenced OS at univariate analysis. Portal

Table 3. univariate analysis

	Disease free survival		Overall survival	
	Hazard ratio (95%CI)	**P-value**	**Hazard ratio (95%CI)**	**P-value**
Age ≥ 65 years	1.18 (0.81-1.73)	0.40	1.55 (0.93-2.56)	0.09
Portal vein embolization	1.78 (1.03-3.09)	**0.04**	2.52 (1.34-4.78)	**<0.01**
CEA > 200 ng/mL	1.78 (0.90-3.53)	0.10	2.90 (1.31-6.43)	**<0.01**
Rectal site of primary tumor	0.83 (0.57-1.22)	0.35	1.05 (0.64-1.74)	0.85
Lymph node positive primary	1.10 (0.74-1.61)	0.65	0.72 (0.43-1.20)	0.21
Largest lesion >50 mm	0.94 (0.61-1.45)	0.78	1.15 (0.66-1.98)	0.63
Number of lesions				
> 1	1.30 (0.89-1.89)	0.17	1.44 (0.87-2.38)	0.16
> 3	1.66 (1.06-2.58)	**0.03**	1.58 (0.87-2.87)	0.14
Disease-free interval < 12 months	1.51 (1.00-2.28)	**0.05**	1.53 (0.86-2.70)	0.15
Fong score 3-5, high clinical risk	1.64 (1.11-2.42)	**<0.01**	1.35 (0.80-2.275)	0.26
No ischemia	Indicator		Indicator	
Mild ischemia	1.00 (0.50-2.00)	1.00	1.13 (0.48-2.68)	0.78
Severe ischemia	1.93 (1.23-3.02)	**<0.01**	2.12 (1.18-3.80)	**0.01**
Major hepatectomy	1.08 (0.73-1.58)	0.71	1.10 (0.66-1.82)	0.72
Non radical resection	1.38 (0.86-2.22)	0.19	2.13 (1.21-3.77)	**<0.01**
Intraoperative transfusion	1.30 (0.82-2.04)	0.26	2.15 (1.28-3.63)	**<0.01**
Preoperative chemotherapy	1.50 (0.92-2.43)	0.11	1.20 (0.65-2.21)	0.56
Simultaneous primary tumor resection	1.13 (0.66-1.96)	0.66	0.87 (0.37-2.02)	0.75

Table 4. Multivariate analysis

	Disease free survival		Overall survival	
	Hazard ratio (95%CI)	**P-value**	**Hazard ratio (95%CI)**	**P-value**
Fong score 3-5, high clinical risk	1.60 (1.08-2.36)	**0.02**		
No ischemia	indicator			
Mild ischemia	1.04 (0.52-2.07)	0.93		
Severe ischemia	1.89 (1.21-2.97)	**<0.01**		
Portal vein embolization			2.55 (1.35-4.83)	**<0.01**
Intraoperative transfusion	-	-	2.55 (1.39-4.37)	**<0.01**
Age ≥ 65 years	-	-	1.80 (1.07-3.06)	**0.03**

vein embolization (HR 2.55 (1.35-4.83), P < 0.01), intra-operative transfusions (HR 2.55 (1.39-4.37), P < 0.01), and age > 65 years (HR 1.80 (1.07-3.06), P = 0.03) were independent predictors for OS (table 4).

DISCUSSION

In the present study, intermittent VIO with severe ischemia during resection of CRLM was identified as independent predictor of reduced DFS without affecting OS. It remains, however, unclear what the clinical impact of these finding should be especially considering intraoperative blood transfusion was also related with OS in multivariate analysis.

Hepatic VIO has been employed during liver surgery for many decades and the cumulative duration of ischemia considered as safe has increased over time.[9,21] Although VIO has proven effective during liver resection in reducing intra-operative blood loss and the need for transfusion and consequently, postoperative morbidity, there is a vast amount of literature on the adverse effects of VIO. VIO induces hepatic IR injury, which has been studied extensively in both animals[22,23] and humans.[15,24,25] The induced sterile inflammation compromises postoperative liver function through hepatocellular necrosis[10] but also induces effects remote from the liver. Post-operative kidney injury,[26] pulmonary injury,[27] gut injury,[28] pancreatic injury,[29] and even myocardial injury[30] have all been attributed to hepatic IR. These widespread effects of hepatic IR have also included intra-hepatic tumor growth, tumor invasion, migration and progression of micrometastases in several tumor models.[11-13,31,32] Depending on the operative situation, the benefits of VIO in terms of limitation of blood loss may not always outweigh the potential oncological risks of disease recurrence.

Several studies have addressed the impact of hepatic VIO during resection of CRLM on survival. Like the present study, none of these studies could identify an effect on OS.[14,33,34] In a report on 543 hepatectomies for CRLM, no impact of VIO was found on DFS.[35] The inability to confirm the results from animal models was, in part, attributed to improved neoadjuvant chemotherapy regimens. The present cohort contains more synchronous metastases and more metastases with a rectal origin. Synchronous metastases are associated with a higher risk of recurrence, which could be an explanation for the observed discrepancies.[20] Also, VIO was employed less often in this study which also might account for the different conclusions. Another series of 687 patients found no impact of VIO on DFS, which may be related to the high rates of metachronous metastasis, and the more frequent use of VIO with only a median duration of 22 min.[36] The third report included a case-matched analysis of 120 patients operated for metachronous CRLM only and reported a protective effect of hepatic VIO on recurrence.[15] Although case-matching may reduce the impact of selection bias, the small group of only 120 patients with only metachronous metastases included over the two matched groups out of a larger total of 478 patients might have resulted in a selection bias. Only one other study concluded that severe ischemia (≥ 20 minutes continuous or ≥ 45 minutes intermittent ischemia) results in impaired disease free survival.[16] In this study of 122 patients severe ischemia was associated with increase hepatic recurrence (HR 1.38 (1.04–1.83). The study had a majority of synchronous metastases (69 of 122, 57%), which was also a predictor of both hepatic and overall recurrence, which could account for the different

results in other reports. Although synchronous disease was not a significant independent predictor of liver recurrence in our cohort, it was a predictor of overall and liver recurrence at univariate analysis. Therefore, a majority of metachronous metastases might have been a confounding factor in studies concluding that VIO does not affect DFS.

In the present study, we showed that severe hepatic ischemia is an independent risk factor for reduced (liver) DFS but not OS, indirectly confirming experimental studies pertinent to this issue. In contrast to previous reports, more patients with synchronous metastasis were included and no upfront criteria for patient selection were used. However, our study has some limitations. Firstly, the present study is a retrospective analysis which is always subject to selection bias. Secondly, the present study including 208 patients is relatively small compared to the previous studies which included 80-2114. patients.[14,34] Notwithstanding these limitations, the present results encompassing more synchronous metastases compared to previous reports warrant future prospective cohort studies to re-examine application of VIO in the context of recurrence.

Although any application of VIO was also a predictor of DFS, the ischemia variable was separated into no, mild, or severe ischemia in the current analysis. VIO cannot always be avoided and is useful to prevent excessive blood loss and subsequent transfusions. The current study suggests that when VIO is indicated to control blood loss, as short as possible duration of VIO should be preferred in order to limit the impact of ischemia on DFS. Furthermore, considering the adverse effects of VIO, strategies such as transection during low central venous pressure might aid in preventing the need for VIO.[37]

The increased outgrowth of micrometastases induced by severe ischemia might explain current findings on recurrence following resection.[11,16] Interestingly, transfusion was associated with impaired survival in the current analyses whereas VIO is employed to reduce blood loss and transfusion. This antagonism suggests complex interactions between these variables and further research should address the mechanisms, interplay and clinical validity of these concepts. While VIO might be essential in the case of major intraoperative blood loss, it might be undesirable to employ VIO in uncomplicated cases.

In conclusion, application of hepatic VIO resulting in severe ischemia during liver resection for CRLM was associated with reduced DFS, while intraoperative red blood cell transfusion was associated with reduced OS. Therefore the benefits of applying VIO during resection must outweigh the oncological risks besides other risks such as impaired remnant liver function. This requires a patient tailored approach.

Conflict of interest

No conflicts of interest.

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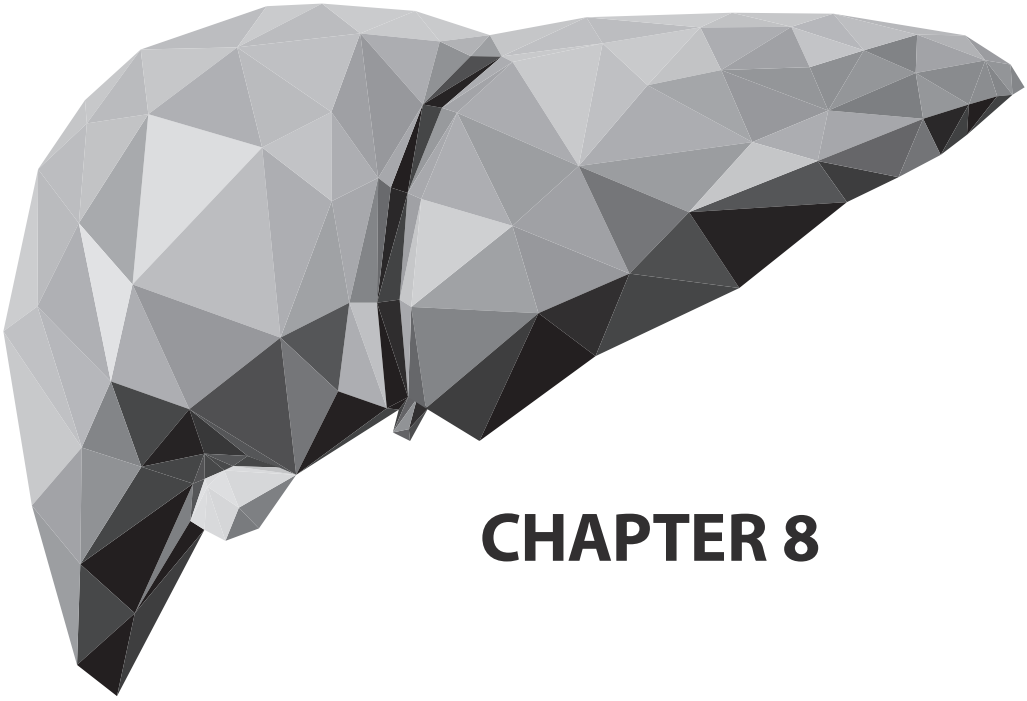
PART II



CHAPTER 8

Local approval procedures act as a brake on RCTs

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ABSTRACT

Aim

The logistics of initiating clinical research in the Netherlands are becoming increasingly complex. In the current study, the procedures for obtaining approval for local feasibility of two national investigator-initiated, multicentre phase 3 studies in colorectal cancer were evaluated.

Design

retrospective, descriptive.

Method

The time intervals between the approval by the central Medical Ethics Committee (MEC) for participation and the receipt of the application file by local centres as well as the receipt of the written local approval were examined for two investigator-initiated studies: CAIRO5 and CHARISMA of the "Dutch Colorectal Cancer Group". The number and type of requested documents by each centre and the amount of any fees charged for this procedure were evaluated.

Results

A total of 28 procedures were analysed. The median time interval between the approval by the central MEC for participation and the final approval for local feasibility by the Board of Directors was 90 days (range 4-312). The median time interval between receipt of the application file by a participating centre and their written confirmation of local approval was 21 days (range 3-178). The median number of requested documents was 10 (range 6-20). The charges by participating centres for this procedure was on average € 318 (range 0-1,750).

Conclusion

Our analysis of the procedures for obtaining approval for local feasibility of participating centres concerning two Dutch multicentre studies, showed a large variety in time, content and costs. This seriously hampers the conduct of clinical research, and therefore urgently warrants more simple and uniform regulations.

INTRODUCTION

Prospective randomised trials are considered the best instrument to test the effectiveness of medical interventions and is therefore at the core of 'evidence-based' healthcare. Novel treatment modalities are currently emerging with increased frequency, which results in a great demand for these trials. [1]. This research typically involves a large number of patients, and therefore the participation of multiple centres. In 2014, 759 multicentre studies were assessed by a medical ethical committee (MEC) in The Netherlands, of which 43% were investigator-initiated studies [2]. The initiation and conduct of these multicentre studies require a significant investment of time and money. This is especially an obstacle for investigator-initiated research, which unlike pharmaceutical industry-driven research typically has no structural financial and staff support.

Central medical ethical approval and subsequent local approval of the participating centres for feasibility are required before a trial can be initiated. The increasing complexity and diversity of the procedure to obtain approval for local feasibility causes delay and increases costs [3-8]. This hampers the conduct of clinical research in The Netherlands [2, 9]. However, objective data regarding this issue from practical experience are scarce [3, 4, 6].

The so called 'Richtlijn Externe Toetsing' (RET; Guideline for External Assessment) is the Dutch guideline in which the rules are described for the procedure to obtain approval for local feasibility by a local centre. The guideline is prepared by the Central Committee on Research Involving Human Subjects of the Netherlands (CCMO) [10]. The scope of this directive is limited in terms of its influence on local levels (individual research institutions). The RET is endorsed by the Boards of Directors of University Medical Centres (UMC) and the Cooperating Top Clinical Medical Teaching Hospitals (Samenwerkende Topklinische opleidingsZiekenhuizen, STZ). These hospitals have expressed their endorsement of the RET by signing the so called 'Institution Statement' [11, 12]. The RET and the Institution Statement contain the following mandatory aspects: 1) to provide a signed "research statement" of the local researchers and the facilities by a participating centre for assessment by the central Medical Ethical Committee (MEC) [13]; 2) an insurance for subjects of each participating centre; and 3) substantive scientific assessment of the study protocol and patient information leaflet may only be done by the central MEC and not by the participating centres. Other aspects of the local procedures at the level of a participating centre such as the duration, charges and content of the process are not regulated by the CCMO (and the CCMO is not allowed to do so). The Institution Statement only stipulates in general that local centres should have efficiently organized their applications for participation in multicentre trials [11].

The Netherlands ranks internationally among the countries with the highest scientific output, both in volume and quality [14, 15]. One of the most important parameters that determine the success rate of clinical research is the speed by which logistic procedures that

are required for study initiation are completed. This is especially true for pharmaceutical industry-initiated clinical research, in which pharmaceutical companies monitor the procedural and financial parameters of individual countries and centres[9]. In such reports the procedure required for obtaining approval for local feasibility is mentioned as a cause of declining attractiveness at an international level to carry out multi-centre clinical trials in The Netherlands [9]. The feasibility of multicentre research can be facilitated by standardization of this procedure. Data from The Netherlands and other countries specifically indicate a delay caused by the local feasibility procedures, confirming that these procedure are complex and difficult to optimize in terms of efficiency and costs [14, 16-24].

In the current study we have evaluated the procedure for obtaining approval for local feasibility of the participating centres of two investigator-initiated, multi-centre randomised trials of the Dutch Colorectal Cancer Group (DCCG): CHARISMA and CAIRO5 [25, 26]. The purpose of our evaluation is to provide real-life data on this issue and thereby to contribute to the development of a more efficient, less costly and uniform procedure.

METHODS

The CHARISMA and CAIRO5 trial evaluate treatment strategies for patients with colorectal liver metastases [25, 26]. The CHARISMA trial was reviewed by the MEC of the Erasmus Medical Centre, Rotterdam, The Netherlands, and the CAIRO5 trial by the MEC of the Academic Medical Centre, Amsterdam, The Netherlands.

The procedure

Figure 1 provides an overview of the full procedure for medical ethical approval and approval for local feasibility in participating centres.

The time period that was involved in obtaining local approval in participating centres was evaluated based on four periods:

A. The time period starting from the date of central approval of the MEC to include a new participating centre in the trial up to the date at which official approval was obtained from the local board of directors of each participating centre.
B. The time period between the date of central approval of the MEC to include a participating centre in the trial and the date of submission of the complete file to the board of directors of each participating centre.
C. The time period between the date of submission of the complete file to the board of directors of each participating centre and the date of local approval to start the trial.

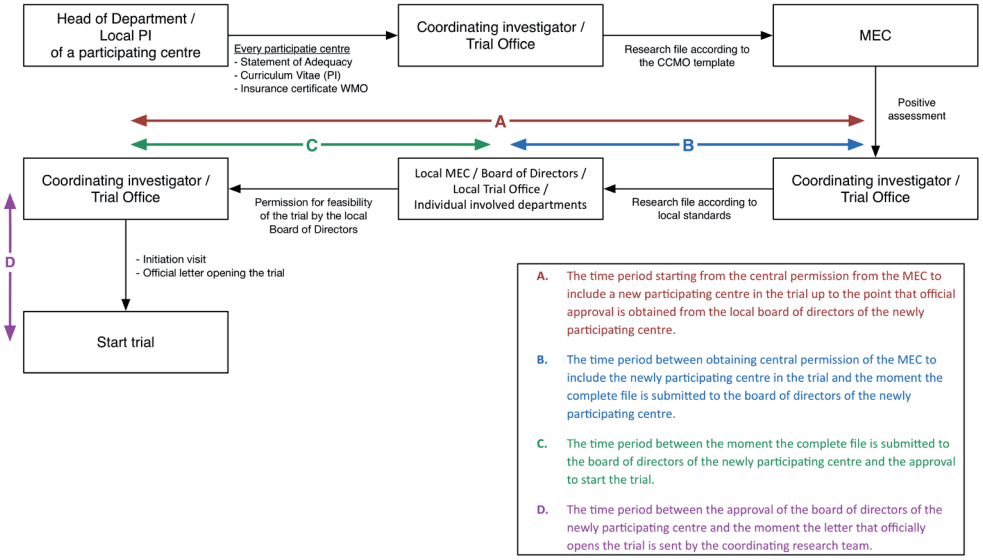


Figure 1. Overview of the procedure for obtaining approval to start a multicentre clinical trial in a participating hospital

D. The time period between the date of approval of the board of directors of each participating centre and the date of written confirmation by the coordinating research team that the trial was open for inclusion.

The procedure for obtaining local approval in each centre was also evaluated according to the following:

- The number and type of documents required for the local procedures that were requested per centre. We specifically kept track of the obligation to deliver a Clinical Trial Agreement (CTA) and a "Good Clinical Practice (GCP)" certificate or "Basic Rules and Organization for Clinical researchers (BROK)" from the local principal investigator;

- Any fees charged by the local MEC for the procedure.

RESULTS

At the time of this analysis the CHARISMA trial was open in 9 centres and the CAIRO5 trial in 19 centres.

Table 1. The median and range of time periods A, B, C and D (days) of all procedures in both trials and of CAIRO5 and CHARISMA trial, respectively.

Time period	Days	
	Median	**Range**
A:		
All procedures	90	4-312
CAIRO5	136	4-312
CHARISMA	63	32-217
B:		
All procedures	64	2-308
CAIRO5	91	2-308
CHARISMA	60	15-116
C:		
All procedures	21	3-178
CAIRO5	21,5	3-178
CHARISMA	17	3-315
D:		
All procedures	68	3-351
CAIRO5	113	3-351
CHARISMA	41	9-78

Time periods

The median and range of time periods A, B, C and D are displayed in table 1. For primary medical ethical review, an initial maximum of 60 days is allowed for the Medical Ethical Committee to assess a study protocol [27]. Therefore, a 60-day time period was chosen as a reference in our analyses. Time period A took more than 60 days in 68% of all procedures. Figure 2 displays the variation in time period A between the CHARISMA and CAIRO5 trials in centres that were open for both trials. Time period B included most of time period A. This period took more than 60 days in 46% of all procedures. Time period C took more than 60 days in only 21% of procedures.

Documents

The median number of documents that were requested per centre for the procedure was 10 (range 6-10) and did not differ between CHARISMA and CAIRO5 (range 7-16 and 6-20, respectively).

A CTA was mandatory in 69% of the centres, and 65% of the centres requested a certificate of good clinical practice (GCP). Notification in the curriculum vitae of the local investigator that the GCP certificate was obtained was often considered as sufficient.

In case the local committee demanded that any standard file had to be adjusted it predominantly concerned the CTA and/or the patient information leaflet. The type of modifications of CTA that were requested differed greatly among centres. Also, local centres

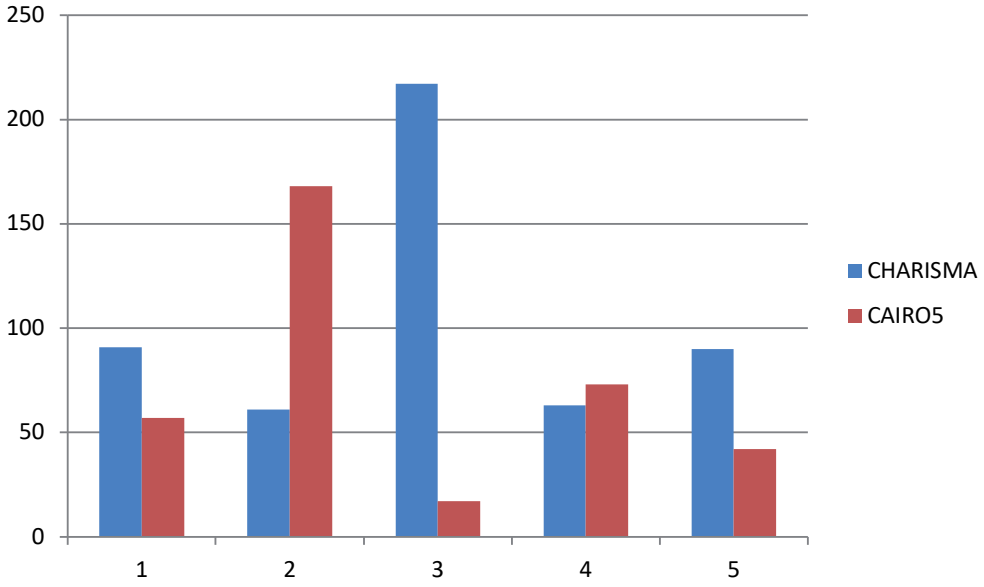
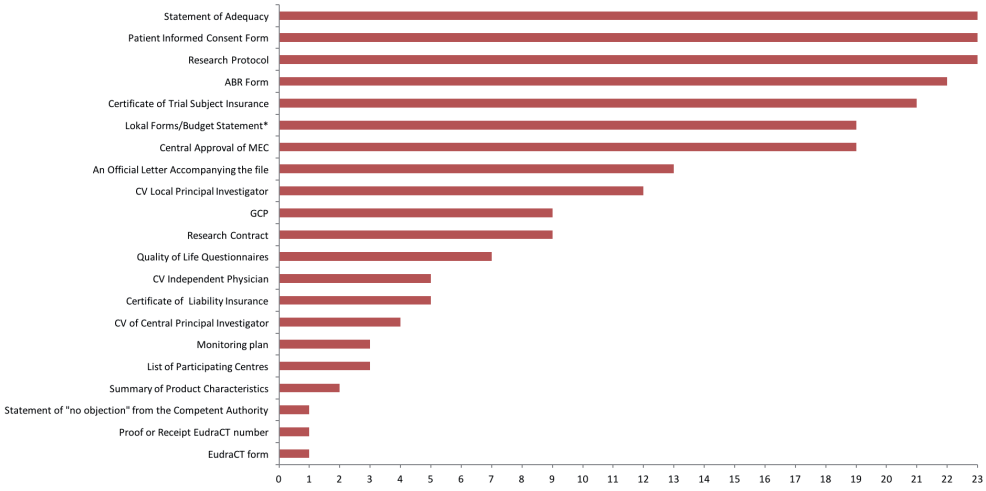


Figure 2. The variation in time period A in 5 centres that were open for both the CHARISMA and CAIRO5 trial. X-axis: centres, Y-axis: time period in days.



** local budget form or other local forms designed by participating centres; Procedures were analysed in a total of 23 centres.*

Figure 3. Overview of types of documents that participating centres requested for their local approval procedures. X-axis: number of centres, Y-axis: document type.

often required additional documents, such as an estimate of radiological diagnostics or laboratory tests that may or may not take place in the context of the trial. Documents that are required by supportive departments could cause delay of the procedure. Figure 3 displays the different types of documents that were involved in all procedures.

Fees

The average fee charged for the procedure was € 318, with a range of € 0-1,750. 62% of the centres charged no costs for the procedure.

For CAIRO5 the mean fees were €226 with a range of € 0-1,750, the total fees were € 4,075. For CHARISMA the mean fee was € 500 with a range of € 0-1,750, the total fees were € 4, 500.

DISCUSSION

Our analysis demonstrates that the procedure for obtaining approval of local feasibility in participating centres to multicentre trials greatly varies in duration, content and charges of procedures.

In 2012 a new guideline for external validation (RET 2012) was drafted in the Netherlands, and this guideline is operational since 1st of March 2012 [10]. The foremost modification in the guideline was the abolition of the ''local feasibility statement'', which implied that a reassessment of the content of the trial protocol by the local centre should no longer be performed. The track for obtaining approval of local feasibility for multicentre research has been re-evaluated by research groups and by the CCMO after implementation of the new guideline in 2012 [3, 6, 7]. The mean time lapse between obtaining approval by the central MEC and obtaining approval by the board of directors of the local participating centre was 50 days for centres who adhered to the new guideline and 118 days for those who did not [3]. In our study the mean time lapse of this procedure was 90 days.

Results from an evaluation by the CCMO showed that within 60 months 50% of the centrally approved studies were opened for inclusion of patients in a participating centre [6, 27, 28]. In our study this percentage is 32%. In contrast to central medical ethical reviews of clinical research, the procedure for local approval has no time limit.

The time period between the date of submission of the complete file to the board of directors of a participating centre and the date of local approval to start the trial is relatively short. An explanation for this phenomenon is the introduction of the RET 2012 (abolishment of a double review). From a researcher's perspective however, the delay now occurs between the date of central approval of the MEC to include a participating centre in the trial and the date of submission of the complete file to the board of directors of a participating centre. This period cannot be influenced by the RET 2012 or the CCMO. Our study demonstrates that the period of time of the total procedure has not been shortened. The CCMO also suggested this in their review [6, 28].

Lastly, we observed a delay between the date of final local approval and the date of dispatch of the letter by which the trial is officially open for accrual. This however is the

responsibility of the research teams and not of the participating centres or local medical ethical committees, and is not part of the RET 2012.

The Procedure

In 2012 the local feasibility statement was replaced by the "research statement". The research statement has to be signed by the head of department/healthcare group manager/local researcher on behalf of the participating centre [13]. However, departments that are not directly involved in the primary care of study patients, i.e. diagnostic departments such as radiology, clinical laboratory and pathology, are usually not involved in an early stage of the local approval procedure. This often results in a delay when the local approval procedure is further advanced and these departments are confronted with study procedures that involve their collaboration. The use of a uniform procedure using standard formats that is initiated as soon as a local centre shows interest in trial participation would prevent unnecessary delays.

Documents

We observed a large variation among centres in the number of documents that were requested for local approval. There is no national standard research file in The Netherlands for this procedure such as exists for the procedure of central approval by the medical ethics committee.

Handling of the CTA is causing an important delay in the procedure. This was also recognized in the evaluation by the CCMO [6, 28]. Of note, not all centres require a CTA. The CTA is a frequent cause of time-consuming correspondence between the legal departments of the initiating organization/centre and the local centres. In The Netherlands a CTA between the initiating party and participating centres is not mandatory by law, and there is no uniformity regarding the content of CTA. Several CTA templates are available, however these have been drafted by different authorities and show substantial disparities (CCMO [29], STZ-Nefarma-ACRON-NKI [30]). We observed significant differences among participating centres in the items which their legal departments requested to modify.

Because a GCP certificate is legally not mandatory for local investigators, these were not always available [31]. Where legislation is not available or multi-interpretable the Dutch Federation of University Medical Centres (NFU) academic hospitals together contributes to its development. In case of the GCP certificate the NFU urges to make this mandatory [32]. This lack of a requirement for a GCP certificate is a cause for delay. A clear statement on this issue in the CCMO guideline would facilitate this process.

Financial compensation

Despite the signing of the 'Institution Statement' by 8 academic hospitals and 27 Cooperating Top Clinical Medical Teaching Hospitals [12], 38% of the hospitals charged

widely varying fees for the procedure of local approval. The Institution Statement only mentions that participation in multicentre research should be organized and supported as efficiently as possible, and the issue of charges is not mentioned. The observed variation in fees is illogical and undesirable, especially for investigator-initiated studies which usually have a limited budget. We support a procedure that is free of charges or a procedure with transparent and uniform costs, taking the nature of the study into account (investigator- versus pharmaceutical industry-initiated).

CONCLUSION

Great variation exists in the procedures for obtaining approval for local feasibility of multicentre research in terms of time, content and costs. These variations are unpredictable and pose a serious obstacle in conducting scientific clinical research in The Netherlands. Delay in the process of initiation of studies decrease the chance of successful accrual of patients and thereby endanger their successful completion. This is not acceptable from the perspective of patients, researchers and funding bodies. This process is not within the scope of the RET 2012. Consensus on simplification of the procedure is urgently warranted. Collaboration with all stakeholders on further standardization, centralization and digitalization of the procedure would be of great value. Currently three Dutch cancer research groups, the Dutch Colorectal Cancer Group (DCCGH), Breast Cancer Research Group (BOOG), Hematology Oncology Research group (HOVON), in collaboration with the Dutch Comprehensive Cancer Centre (IKNL) and Dutch Cancer Foundation (KWF) are initiating the establishment of a national platform (Dutch Oncology Research Platform, DORP) which aims among other issues to coordinate and create uniformity in logistical procedures that are involved in investigator-initiated clinical cancer research in The Netherlands.

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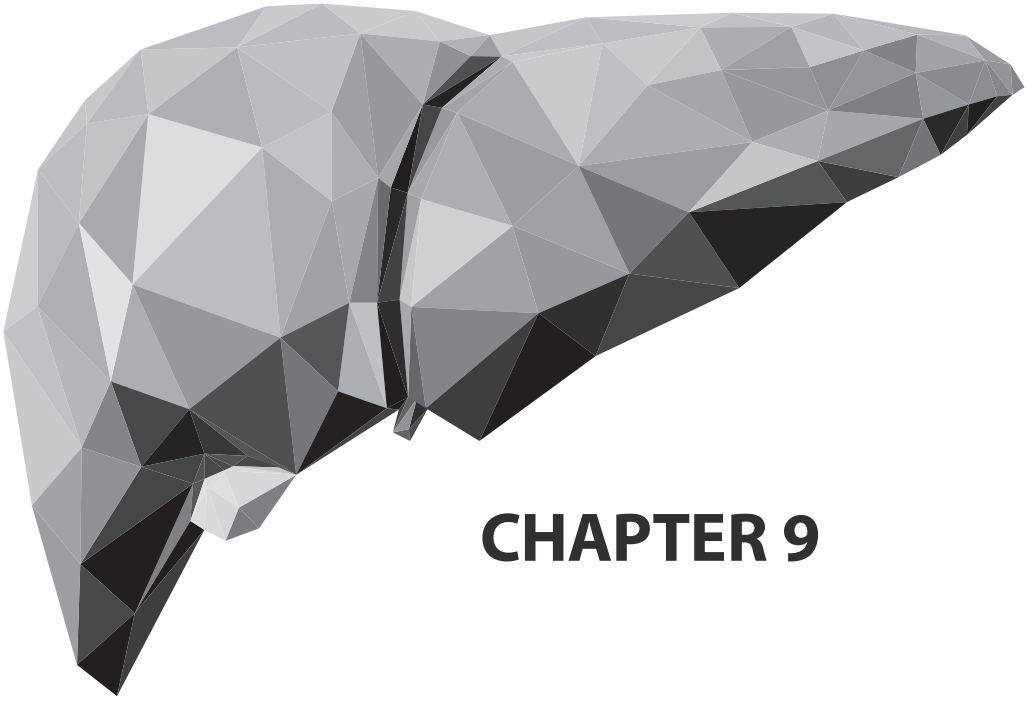

CHAPTER 9

From registration to publication; a study on Dutch academic randomized controlled trials

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ABSTRACT

Introduction

Registration of clinical trials has been initiated in order to ensure adherence of the reported results to the original trial protocol. This study aimed to investigate the publication rates, timely dissemination of results and the prevalence of consistency in hypothesis, sample size and primary endpoint of Dutch investigator-initiated randomized controlled clinical trials (RCT).

Methods

All Dutch investigator-initiated initiated RCTs with a completion date between 31th December 2010 and 1st of January 2012 and registered in the Trial Register of The Netherlands database (NTR) were included. PubMed was searched for the publication of these RCT results until September 2016 and the time to the publication date was calculated. Consistency in hypothesis, sample size and primary endpoint compared with the registry data were assessed.

Results

The search resulted in a total of 168 Dutch investigator-initiated RCTs. In September 2016, the results of 129 (77%) trials had been published, of which 50 (39%) within 2 years after completion of accrual. Consistency with the original protocol was observed in 108 (91%) RCTs, in 71 trials (55%) the planned sample size was reached, and 101 trials (80%) presented the original primary endpoint. Consistency in all three parameters was observed in 50 studies (39%).

Conclusion

This study shows that approximately one out of four Dutch investigator-initiated RCTs remains unpublished five years after initiation. The observed low overall consistency with the initial study outline is a matter of concern, and warrants improvements in trial design and assessment of trial feasibility.

INTRODUCTION

The declaration of Helsinki (1964) is the corner stone of modern human research ethics. Based on the fundamental principle of respect for the individual and the right to take informed decisions regarding participation in research, the declaration morally binds physicians and scientists to publish clinical trial information and results.[1] It has been estimated that only half of the one million trials started since 1948 have been published.[2]

Patients who give informed consent to participate in scientific research and thereby agree to exposure to an experimental treatment do so under the assumption that they contribute to medical science. If investigators fail to publicly communicate these results this contribution is nullified and the conditions for the initial agreement for participation are not met. This implies that invaluable information for the selection of optimal treatment and for the allocation of future research funds are withheld from the scientific community. This also results in loss and distortion of evidence, impairment of the practice of evidence-based medicine and a potential waste of funds on duplicative trials. Failure to publish research results has been considered as scientific misconduct.[3, 4]

The validity of clinical trial results start with a carefully designed and conducted trial. Adherence to the trial protocol in the eventual trial report is essential in minimising bias and prevention of selective reporting. Reporting of results based on outcomes or any specific interest of the investigator, will increase the risk of bias and potentially hampers evidence-based medicine. Unfortunately, discrepancies between a registered trial protocol and its publication are still frequently reported.[5–8]

Since July 2005, the International Committee of Medical Journal Editors (ICMJE) requires trials to be registered before the enrolment of the first patient in order to prevent selective publication of trial outcomes in an effort to reduce this form of publication bias.[9] Besides the obligation to publish trial results, it is essential that these results become available within an appropriate period to ensure that clinical decisions can be made on the most recently available evidence. However, since 2005, several reports have shown that between 25% and 50% of the clinical trials experience significant delay or even remain unpublished. [8, 10–16] The tendency to publish only positive results is just one of the reasons many trials remain unpublished.[17]

Even though academic medical centres are at the heart of clinical research, their publishing and reporting of results is not optimal.[14, 16, 18, 19] In The Netherlands there is an excellent track record of investigator-initiated clinical research which is considered due to a well organised research infrastructure in which academic and general hospitals are actively participating.[20]

This study aims to investigate the rates of publication of trial results within two years after planned completion or premature closure of patient accrual. The prevalence of consistency in hypothesis, sample size, and primary endpoint between the registry and

the corresponding publication of Dutch investigator-initiated randomized controlled trials (RCTs) was investigated.

METHODS

In August 2016, information of all RCTs registered in the prospective Trial Registry in The Netherlands (NTR), which is part of the WHO primary registries, was collected. To ensure an adequate period allowing researchers to publish their results, only RCTs with a reported completion date between 31 December 2010 and 1 January 2012 were included. To identify all RCTs with a responsible party based at a Dutch academic medical centre the 'SPONSOR/INITIATOR' field of the NTR was used. All RCTs that had one of the eight Dutch academic medical centres submitted in this field were selected for analysis. Multicentre and multinational trials were included only if a Dutch academic centre had initiated the trial. Of every RCT the sample size, the study design (single or multi centre design) and the studied condition according to the clinicaltrials.gov categories were collected.

The outcome parameters included the number of published RCTs, the number of RCTs with published results within two years after completion of patient accrual, and the consistency between the trial registry data and published data was scored in respect of the main hypothesis, sample size and primary endpoint.

Search strategy to identify publication of RCTs

The PubMed service was used to search the biomedical literature for publication using the unique registration numbers of the RCTs between January 2011 and September 2016 by two reviewers (BK and JH). If no publication was identified, the search was expanded with details of the registered trial, such as author, acronym, primary outcome, scientific title and hypotheses. Finally, if still no publication was found, the principal investigators of the study were contacted by email. A reminder was sent to every contact person that did not respond to the first email within one week. If no publication was found, and if the principal investigators did not reply to either email, it was assumed that the trial results had not been published.

The earliest publication of a RCT reporting the main results including the primary endpoint was selected. If multiple primary endpoints were registered, the earliest publication reporting at least one of the primary endpoints was used to assess the time to publication. All articles were retrieved by BK, and a second reviewer JH independently reviewed all selected articles. Any uncertainties were discussed until consensus was reached. In case BK was not able to identify the publication of a registered RCT, a second search was performed independently by JH.

Data selection of published trials

Full copies of all identified articles were obtained and the time-span in months between the completion date and the publication date was calculated using the 'completion date' field of the NTR database and the publication date. For RCTs with an earlier online publication date (ePub date) the ePub date was used as the publication date. The following variables were collected from the available publications: the hypothesis, sample size and the primary outcome.

Assessment of consistency: comparison of publications with their protocol

All retrieved corresponding publications of registered RCTs were used for the consistency assessment. Consistency in hypothesis was assessed by comparing the primary hypothesis provided in the NTR with the hypothesis in the published article. When a hypothesis was not provided in the NTR, that RCT was recorded as discrepant in hypothesis for the analysis. In case multiple primary endpoints were registered, a RCT was only considered consistent in primary endpoint if all primary endpoints were published and no new primary endpoints were provided in the publication. The primary endpoint was also considered discrepant if it was not reported in the NTR.

It is mandatory in the NTR to register the sample size of a trial. The sample size calculation was considered discrepant if the sample size calculation of the publication differed from the NTR. When no sample size calculation was provided in the publication, and the recruited number of patients did not differ more than 5% from the registered sample size, the trial was considered consistent in sample size calculation.

If a published hypothesis, primary endpoint and/or sample size showed discrepancy with the information as registered in the NTR but a transparent and clearly formulated explanation for the deviation was provided in the publication, the RCT was considered consistent on this issue.

RESULTS

Between December 31th 2010 and January 1st 2012, a total of 168 RCT sponsored by a Dutch academic centre were registered in the NTR. These 168 RCT had a total sample size of 55.821 patients (median 120, IQR 50-264). Among the 168 RCT, 67 (40%) had a multi-centre design and 87 (52%) were planned to enroll more than 100 patients. Nutritional and metabolic disorders (18%), disorders in behaviour (18%), cancer and other neoplasms (11%), and cardiovascular diseases (11%) were the most frequently studied conditions. Additional RCT characteristics are summarized in Table 1.

Table 1.*Overall characteristics and dissemination of randomised controlled trials across Dutch academic centres. (completion date between 31th December 2010 and 1st of January 2012)*

	Trials registered N	Overall rate of publication N (%)	Median time from completion date to published results in months (IQR)	Rate of results published ≤24 months of study completion date N (%)
Total	168	129 (77)	30 (19-43)	50 (20)
Center				
I	29	24 (83)	29 (16 – 41)	9 (31)
II	28	21 (75)	24 (21 - 43)	11 (39)
III	16	15 (94)	22 (10 – 45)	4 (25)
IV	24	17 (71)	25 (15 – 48)	9 (38)
V	21	15 (71)	25 (15 – 47)	7 (33)
VI	10	8 (80)	33 (22 – 44)	2 (20)
VII	13	11 (85)	44 (27 – 53)	2 (15)
VIII	27	18 (67)	32 (19 – 42)	6 (22)
Study sites				
Multicenter	68	51 (75)	33 (18 - 52)	18 (35)
Singlecenter	100	78 (78)	29 (19 - 40)	32 (41)
Number of enrolled patients				
≤ 100	80	62 (78)	30 (18 – 46)	22 (35)
> 100	88	67 (76)	31 (19 – 43)	28 (42)
Conditions studied				
Nutritional and metabolic disorders	30	24 (80)	28 (15 – 36)	11 (46)
Behaviour disorders	30	23 (77)	25 (16 – 36)	11 (48)
Cardiovascular diseases	19	14 (74)	29 (18 – 34)	5 (36)
Cancer and other neoplasms	19	16 (84)	27 (21 – 35)	7 (44)
Nervous system diseases	10	7 (70)	47 (19 – 55)	3 (43)
Muscle, Bone and Cartilage diseases	9	6 (67)	32 (12 – 46)	2 (33)
Conditions of the urinary tract, sexual organs, and pregnancy	9	6 (67)	47 (33 - 58)	0 (0)
Wounds and Injuries	7	7 (100)	48 (39 – 59)	1 (14)
Viral diseases	5	5 (100)	36 (25 – 53)	1 (20)
Respiratory tract diseases	4	1 (25)	32 (32 – 32)	0 (0)
Infectious diseases	4	2 (50)	15	1 (50)
Digestive system diseases	3	2 (67)	36	1 (50)
Other	19	16 (84)	33 (20 – 45)	7 (44)

Publication of results

In total, 129 (77%) out of 168 RCTs were published in a medical journal as of October 2016 with a median time to publication of 30 months (IQR 19–43). An overview of the publication rate of RTCs is shown in Figure 1. Publication rates varied between the leading academic centres, ranging from 67% to 94%. The rates of RCTs published within 24 months ranged between 20% and 39% (Table 1). In addition, the differences in time to publication between study topic was displayed in figure 1B.

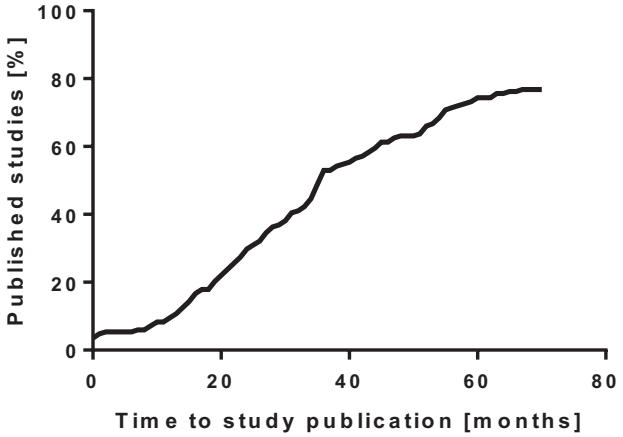

Figure 1. *Rates of publication of randomised controlled trials across Dutch academic centres (closing date 2011)*

A large variety in time between the completion and publication date of a RCT was observed. Results of 50 (30%) RCTs were published within 24 months, and of 79 RCTs (47%) results were published more than 24 months after the completion date. Results of 5 (4%) RCTs were published before their closing date. Figure 2 illustrates the cumulative percentage of completed RCTs with published results.

Of the 39 (23%) RCTs that were not published, 21 principal investigators responded to our emails. Of one RCT, contact information could not be found in the NTR, which leaves 18 (11%) of the 168 RCTs without any information on publication. The principal investigators who replied to our email indicated that 8 RCTs were never published because the RCT had been prematurely discontinued or had never been initiated. Of 6 RCT it was indicated that the conduct had been delayed and consequently publication was delayed. Contacts of 4 RCT responded that the manuscript of their RCT was rejected by journals for publication. One principal investigator was in the process of writing the manuscript and one replied that his PhD student had left and therefore the RCT was never published.

Consistency in hypothesis, primary endpoint and sample size

Consistency in all three parameters was observed in 50 (39%) of the 129 published RCTs. In 108 RCTs (84%), consistency in the main hypothesis was observed. In total, 10 RCTs did not report a hypothesis in the NTR and were assessed as discrepant. Consistency of the published RCT in the primary endpoint was observed in 103 RCT (80%) and in sample size in 71 RCT (55%). In 6 RCT (5%) no sample size calculation was provided in the publication, but the number of recruited patients was within 5% range from the registered sample size. In 32 of the 58 RCT that were discrepant in sample size calculation, the calculated sample size differed from the registered sample size without an explanation. In 26 of the 58 RCT that were discrepant in sample size calculation no sample size calculation was provided in the

Table 2. *Consistency in hypothesis, sample size and primary endpoint of randomised controlled trials across Dutch academic centres (closing date 2011)*

	Trials published N	Overall consistency N (%)	Consistency in hypothesis N (%)	Consistency in sample size N (%)	Consistency in primary endpoint N (%)	Discrepancy in 3 objects (%)
Total	129	50 (39)	108 (84)	71 (55)	103 (80)	3 (2)
Center						
I	24	11 (46)	21 (88)	12 (50)	19 (79)	1 (4)
II	21	10 (48)	18 (86)	15 (71)	17 (81)	0 (0)
III	15	6 (40)	13 (87)	9 (60)	11 (73)	0 (0)
IV	17	3 (14)	14 (82)	6 (35)	14 (82)	0 (0)
V	15	7 (47)	12 (80)	9 (60)	13 (87)	0 (0)
VI	8	2 (25)	6 (75)	4 (50)	5 (63)	1 (13)
VII	11	6 (55)	10 (91)	6 (55)	11 (100)	0 (0)
VIII	18	5 (28)	14 (78)	10 (56)	13 (72)	1 (6)
Study sites						
Multicenter	51	24 (47)	43 (84)	33 (65)	42 (82)	0 (0)
Singlecenter	78	26 (33)	65 (83)	38 (49)	61 (78)	3 (4)
Number of enrolled patients						
≤ 100	62	27 (44)	52 (84)	35 (56)	50 (81)	2 (3)
> 100	67	23 (34)	56 (84)	36 (54)	53 (79)	1 (1)
Conditions studied						
Nutritional and metabolic disorders	24	12 (50)	21 (88)	13 (54)	19 (79)	2 (8)
Behaviour disorders	23	4 (17)	18 (78)	7 (30)	16 (70)	0 (0)
Cardiovascular diseases	14	5 (36)	12 (86)	7 (50)	12 (86)	0 (0)
Cancer and other neoplasms	16	9 (56)	11 (69)	12 (75)	15 (94)	0 (0)
Nervous system diseases	7	4 (57)	6 (86)	5 (71)	6 (86)	0 (0)
Muscle, Bone and Cartilage diseases	6	2 (33)	4 (67)	4 (67)	3 (50)	1 (17)
Conditions of the urinary tract, sexual organs, and pregnancy	6	2 (33)	4 (67)	5 (83)	4 (67)	0 (0)
Wounds and Injuries	7	2 (29)	7 (100)	4 (57)	5 (71)	0 (0)
Viral diseases	5	3 (60)	5 (100)	3 (60)	5 (100)	0 (0)
Respiratory tract diseases	1	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)
Infectious diseases	2	0 (0)	2 (100)	1 (50)	1 (50)	0 (0)
Digestive system diseases	2	1 (50)	2 (100)	2 (100)	1 (50)	0 (0)
Other	16	5 (31)	15 (94)	7 (44)	15 (94)	0 (0)

publication and the recruited number of patients differed more than 5% of the registered sample size.

Of the 129 reported RCT, 57 (44%) recruited 90% or less than the registered planned sample size. Of these 57 trial reports, 29 (22%) did not report a clear explanation for this lower accrual.

Overall consistency as well as consistency in two, one or even none of the parameters varied between academic centres ranging from 14% to 50% (Figure 3). Three RCTs

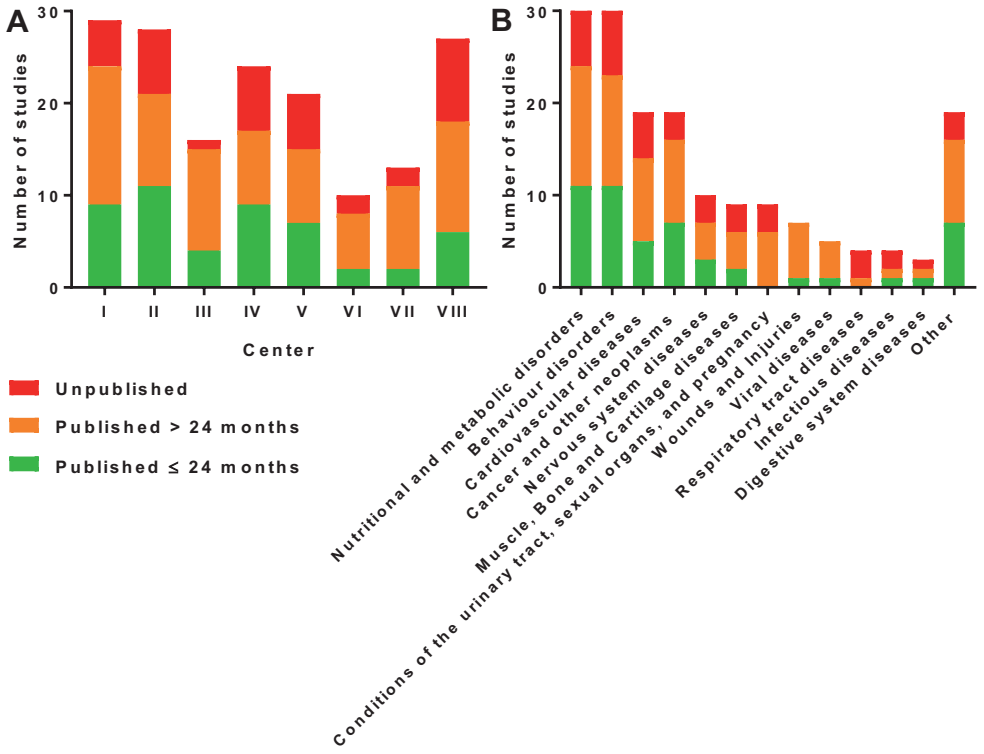

Figure 2. *Time to publication of results for completed randomised controlled trials across (**A**) Dutch academic centres and (**B**) topics (closing date 2011)*

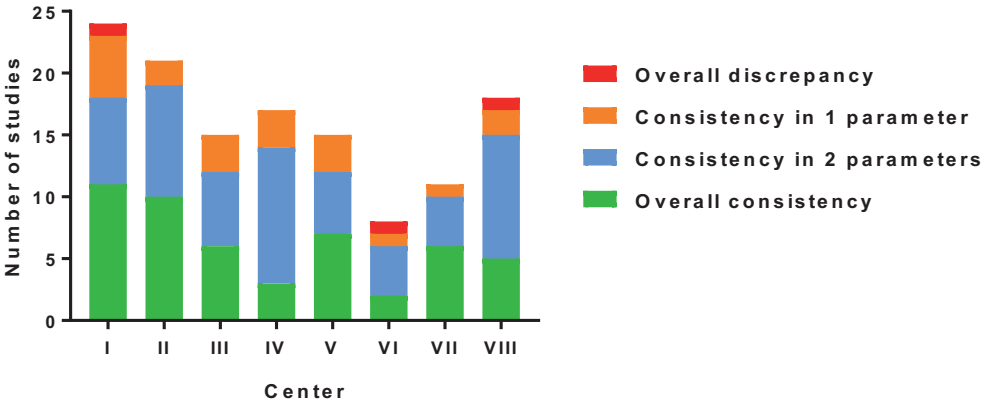

Figure 3. *Rates of consistency in hypothesis, sample size and primary endpoint of randomised controlled trials across Dutch academic centres (closing date 2011)*

demonstrated a discrepancy in all three parameters. There were some differences in consistency between topics, for instance a low sample size consistency (30%) in RCTs on behavioural conditions.

DISCUSSION

A publication rate of 77% among 168 Dutch investigator-initiated RCT within 5 years after the completion of patient accrual of the RCT was observed. Median time to publication was 30 months (IQR 19-43) and only 30% (50/168) of the results were published within two years after the completion date. A low overall consistency in hypothesis, sample size calculation and primary endpoint was found, with only 39% of the 129 published RCTs being consistent in all three parameters. Consistency of sample size reporting was observed in only 55% of the published RCTs.

The observed publication rate of Dutch investigator-initiated RCT is higher than earlier reports.[8, 10–16] However, in this study we found that approximately one out of four Dutch RCT remains unpublished after five years. It seems unlikely that these results will ever be made public. Investigators of these unpublished RCT were planning to recruit a total of 8850 patients. Although the actual number of accrued patients in these unpublished RCT is unknown, a significant number of patients will have been exposed to experimental treatments without any attribution to clinical science. This is in breach of the conditions to which agreement to participation by informed consent was met. Previous investigations have consistently shown that publication bias predominantly affects negative results.[21, 22] There is evidence that non-disclosure of trial results and consequential distortion of evidence is harmful to patients.[23] As an example, in the case of the use of antiarrhythmic drugs for secondary prevention of myocardial infarction, failure of timely publication of negative results has been estimated to have led to up to 75.000 preventable deaths a year in the US alone.[24] Timely reporting of results is essential to support evidence-based decision making by clinicians and patients. To publish results is also essential to allow more selective financing of trials and to prevent waste of funds by avoiding financing of duplicate trials that have proven to produce negative results in the past.

In the present study the principal investigators reported several reasons for not publishing their results. The most common reasons for not publishing were that the RCT had not been started after trial registration or was prematurely discontinued, or that the conduct of the RCT was delayed. Slow patient recruitment is the most common reason for delay. Little evidence is available on strategies to improve recruitment to RCT.[25] A realistic sample size calculation that incorporates the incidence of the studied condition as well as the amount of patients that actually qualify for the trial according to the envisaged inclusion

criteria could help to generate a feasible trial protocol. In this respect, data on accrual of the same patient population in previous trials conducted in the same network would be supportive, since even with data on incidence most investigators overestimate accrual. This implies that innovative tools are needed to improve recruitment. For this purpose, tools that use trial registers as a data repository could improve trial transparency and accrual. [26] Another reason for not publishing was that finalized manuscripts were not accepted for publication by medical journals. This implies that journals contribute to publication bias, which is a known, longstanding but unsolved problem.[27, 28] Publishing results is an ethical obligation of researchers and editors. Withholding results could have major consequences. [28]

A potential solution could be to enable investigators to submit trial results to a trial register. In this way, regardless of publication of the manuscript, the trial results are accessible to the public. However, it is currently not possible to submit study results in the NTR other than in a plain text box. Another possible solution is that research ethical committees could have a more prominent role to ensure that trial results are published by monitoring the conduct of a trial.[29]

The observed low overall consistency in hypothesis, sample size calculation and primary endpoint is a continuous matter of concern.[6, 8] Results of a RCT with discrepancy in hypothesis, sample size calculation or primary endpoint might be unreliable and biased. Changes in trial protocol should be clearly reported and justified, as some may well be well substantiated.

Our study has some limitations. Firstly, only RCT that had a closing date in 2011 were selected. This period was chosen to provide a sufficient window to publish results while the relevance of results that are still not published after 5 years decreases rapidly. Additionally, only RCT were included that were registered in the NTR which is the primary register of The Netherlands, however, Dutch RCT may also have been registered in other registers such as clinicaltrials.gov or ISCRTN.com. Secondly, to find out whether a RCT was published, we ultimately contacted the principal investigators of whom only 51% responded, leaving 11% of the initial RCTs without any information on reasons for non-publication. Finally, the delayed reporting of results may also be due to the publication strategy of the authors, with delays occurring after repeated rejection by journals or due to the required follow-up for the primary endpoint. However, when the required follow-up is not reached it can be debated whether the RCT is really closed and finished. Also, it cannot be excluded that the results of some unpublished studies were presented at conferences without a final publication. Although some might consider this sufficient, this is most often not sufficient to completely review all aspects of clinical trial results.

Recently two national initiatives were launched in order to facilitate researchers in the design, initiation and conduct of clinical trials: the Dutch Clinical Research Foundation

(DCRF)' and 'Dutch Oncology Research Platform (DORP). The possibilities to share research expertise and establish collaborations should reduce the difficulties encountered in the conduct of clinical trials and help improve the timely publication of trial results.[30]

In conclusion, in a sample of 168 investigator-initiated academic RCT, the results of 77% were published within five years. Although this is better than earlier reports, still one out 4 RCTs remain unpublished. The observed low overall consistency is a matter of concern. Publication rates and consistency should be frequently studied to improve the conduction and reporting of RCTs. Solutions are warranted to improve the trial design, trial registration procedures, trial publication rates and consistency between the trial register and publication of a manuscript.

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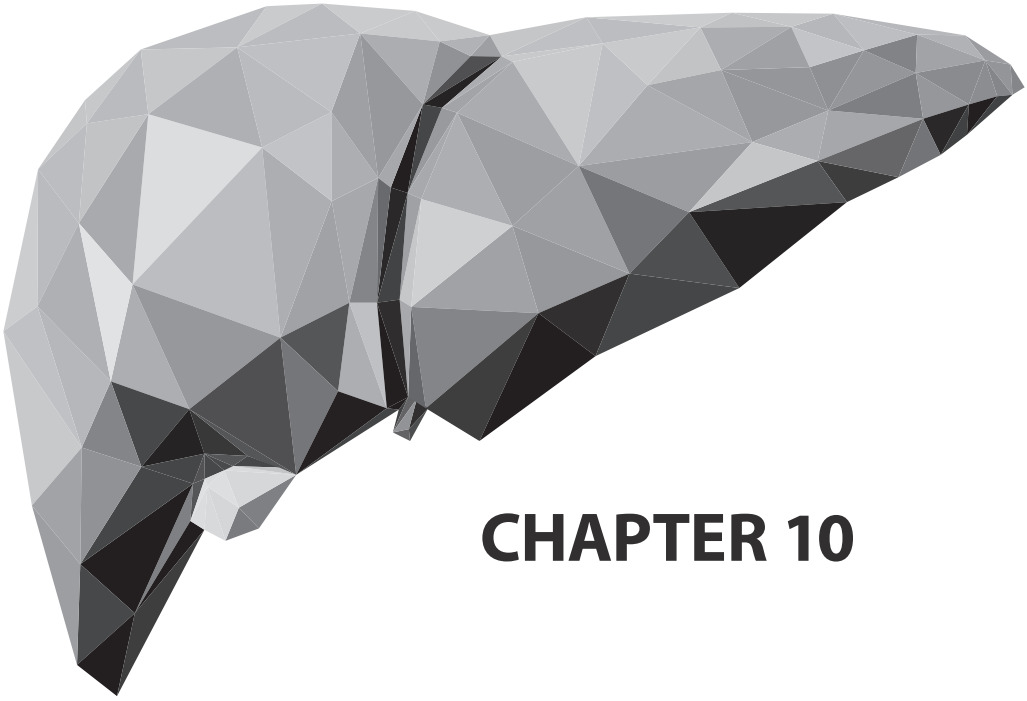

CHAPTER 10

Keeping track of all ongoing colorectal cancer trials using a mobile application: usability and satisfaction results of the Dutch Colorectal Cancer Group Trials app

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ABSTRACT

Introduction

Both the number and complexity of medical trials is increasing vastly. To facilitate easy access to concise trial information, a freely available mobile application including all ongoing clinical trials of the Dutch Colorectal Cancer Group (DCCG) was developed. The aim of this study was to investigate the use and user satisfaction over the first two years.

Methods

The application launched January 2015 on iOS and Android platforms. Google analytics was used to monitor anonymous user data up to February 2017. In addition, an online survey regarding the use and satisfaction amongst healthcare professionals and research affiliates active in the field of colorectal cancer in the Netherlands was conducted.

Results

A total of 6,173 unique users were identified, of which 1,822 (30%) were from the Netherlands, representing a total of 16,065 and 10,987 (68%) sessions, respectively. The median session duration per day was 01:47 minutes (IQR 0:51-03:03). The mobile application was most used on Monday, Tuesday, and Thursday and number of sessions was highest during the following time frames 12-13pm (9%), 17-18pm (9%), and 13-14pm (8%). Out of 121 survey responses, most were medical doctors (47%), nurses (25%), or researchers (9%); working either in a teaching (40%), academic hospital (32%), or general hospital (19%). Eighty-three percent of all respondents rated the application 4 or higher for satisfaction on a 5-point scale. Highest reported reasons of use were: urgent trial inquiry (57%) and usage during multi-disciplinary meetings (49%).

Conclusion

The DCCG Trials App is frequently used and the majority of users is highly satisfied. Clustering trial information into one platform, such as DCCG Trials App, could be useful for medical professionals treating patients with colorectal carcinoma in the Netherlands.

INTRODUCTION

The number of registered clinical trial protocols on clinicaltrials.gov has increased from 12,020 in 2005, to over 230,000 in 2017 and the yearly number of newly registered studies is approaching 30,000. [1] In the field of colorectal cancer alone, the third most common cancer worldwide, 4,482 trials were registered by the end of 2017 (Figure 1).

Besides the increasing number of clinical trials, there has been an increase in protocol design complexity during the past decade. The incidence of added trial protocol amendments is growing and trial criteria are increasingly specified and complex.[2] Among many others, these factors lead to shortage of both knowledge and time for healthcare professionals to participate in clinical trials. [3,4] The complexity of clinical trials can hamper the inclusion of patients, which is the leading cause of problems in the conduction of clinical trials. [5-8] Lack of accrual can lead to trial discontinuation or result in an insufficient sample size, both of which can question the ethics of the exposure of patients to trial treatment which is often outside of routine clinical practice.

Evidence on effective strategies to improve the conduction of clinical trials is scarce and mostly limited to recruitment for randomized trials. [9] The Cochrane systematic review of interventions to improve trial recruitment included 45 studies of which only 12 where considered to be of low risk of bias.[10] Opt-out procedures, telephone reminders and open trial designs might be effective strategies to improve patient recruitment. However, these strategies do not comply with the guidelines of good clinical practice. Interestingly, none of these reported interventions targeted medical doctors, who usually assess patient eligibility for trials and ask patients to participate in clinical trials.

This manuscript illustrates the design of a smartphone application that provides easy to access and up to date information on ongoing Dutch clinical trials for patients with colorectal cancer. The aim of this study is to investigate the usability and satisfaction of the application two years after its introduction.

METHODS

Anonymous user data of the Dutch Colorectal Cancer Group (DCCG) Trials App was collected between the 1th February 2015 and 1th February 2017 and analyzed using Google Analytics. [11] Additionally, an online survey amongst healthcare professionals and research affiliates active in the field of colorectal cancer was conducted.

The DCCG is a research collaboration in the Netherlands between all medical disciplines involved in the diagnosis and management of colorectal cancer. [12] The DCCG Trials App is a mobile application containing concise information on all the DCCG multi-center trials open

for inclusion. The application is freely downloadable for iOS and Android. [13] It can also be accessed through the website: www.trialapp.nl/dccg/dccg-app/ without using the mobile application. Users can find relevant information for the registration of a patient for a trial. Trial coordinators can be e-mailed or called directly via the application for questions. The information provided in the application per trial can be directly updated by the responsible investigators. Trials can be found in two different ways, either by following a decision tree based on clinical features or by utilizing the search function. With the decision tree users can find trials by answering specific question such as; is the tumor located in the colon, rectum, or has the patient metastatic disease? Every trial page has six buttons: design, criteria, requirements, latest news, the trial website, and the contact information. (Figure 2)

Anonymously collected user data by Google analytics [11] included the number of (new) users, the number of sessions, the bounce rate (users that opened and closed the app immediately), average session duration per user per day, geographical location based on IP address, the number and duration of trial information page visits, the number of times the decision tree option was used, and the amount the news option was used.

To measure usability and satisfaction, an online survey was sent either through the DCCG trials app, in the DCCG newsletter researchers and by email using the DCCG mailing list, consisting of email addresses of healthcare professionals and research affiliates. The survey included 10 questions about the respondent's profession, and usability and satisfaction of the DCCG Trials app, using a 5-point Likert scale. For an overview of the online survey see appendix 1.

RESULTS

In its' first two years, the DCCG trials application amassed a total of 16,065 sessions and 89,711 page views by 6,173 unique users worldwide. The median session duration per day was 01:47 minutes (IQR 0:51-03:03). The median number of pages visited per session was 6 (IQR 4-7). In total, the application was used in 102 countries (Supplementary Figure 1).

In the Netherlands, 1,822 (30%) unique users had a total of 10,987 sessions that amounted for 68% of the total sessions of the application. The median average session duration per day in the Netherlands was 02:00 minutes (IQR 01:03-03:30) and the bounce rate was 3% which was the lowest of all countries (Table 1). The mobile application was most used on Monday, Tuesday and Thursday and number of sessions was highest during the following time frames 12-13pm (9%), 17-18pm (9%), and 13-14pm (8%).

Trial information pages were visited 15,896 times and the median time on a trial page ranged from 9 to 47 seconds. The most frequently visited study pages are depicted in Table 2.

Table 1. List of top ten countries in which the application was used

Country	New Users	Sessions	Bounce Rate	Pages / Session	Median session duration (Min)
Netherlands	1822	10987	3%	7,26	02:51
United States	1313	134879	77%	1,47	00:32
(not set)	964	982	87%	1,24	00:18
United Kingdom	418	469	77%	1,92	00:25
China	219	224	82%	1,16	00:38
Japan	149	151	85%	1,17	00:22
Germany	142	169	62%	2,25	00:46
Italy	116	143	34%	3,96	00:40
Brazil	93	95	89%	1,48	00:08
Russia	54	282	48%	1,62	02:59

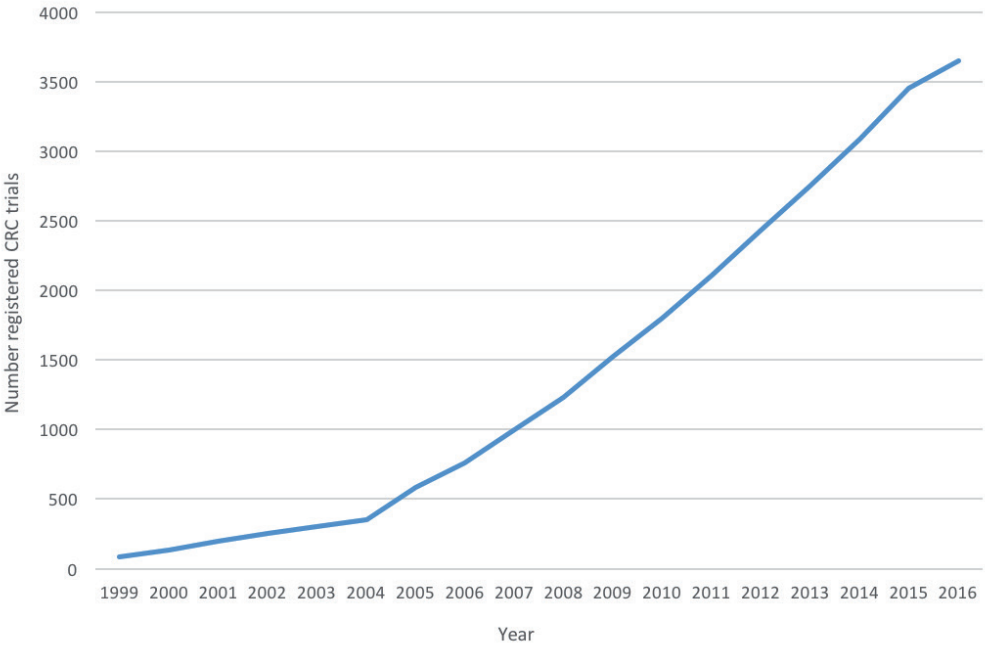

Figure 1. Number of registered trials on colorectal carcinoma in clinicaltrials.gov.

Online survey

Out of a total 121 respondents, 76 (63%) answered that they have used the application, whereas 45 (37%) did not. Reasons for not using the application were unawareness of its existence (n=26, 59%), preference for other resources (n=8, 18%), and that the responder isn't provided a smartphone at work (n=4, 9%) (Figure 3).

Respondents were either medical doctors (n=36, 47%), nurses (n=19, 25%), researchers (n=7, 9%), data manager (n=6, 8%), 8 (11%) of the respondents defined their job as 'other'.

Table 2. All available trials in the application

DCCG Trials	Trial ID	Pageviews: n (%)	Median time on page: sec (IQR)
CAIRO5	NCT02162563	2923 (18%)	47 (18-161)
ORCHESTRA	NCT01792934	2117 (13%)	41 (10-136)
CAIRO4	NCT01606098	1926 (12%)	27 (7-87)
CHARISMA	NTR4893	1591 (10%)	21 (4-74)
COLOPEC	NCT02231086	1575 (10%)	26 (14-71)
RAPIDO	NCT01558921	1125 (7%)	21 (7-58)
ASPIRIN	NCT02301286	1106 (7%)	15 (5-53)
PLCRC	NCT02070146	956 (6%)	11 (5-41)
TESAR	NCT02371304	787 (5%)	19 (5-34)
FIT	NCT02243735	709 (4%)	9 (4-22)
SALTO	NCT01918852	598 (3%)	8 (3-22)
MRI2	NCT01721785	483 (3%)	8 (3-22)
CONSTRUCT	NTR4673	321 (2%)	9 (6-28)
Total		**15896**	

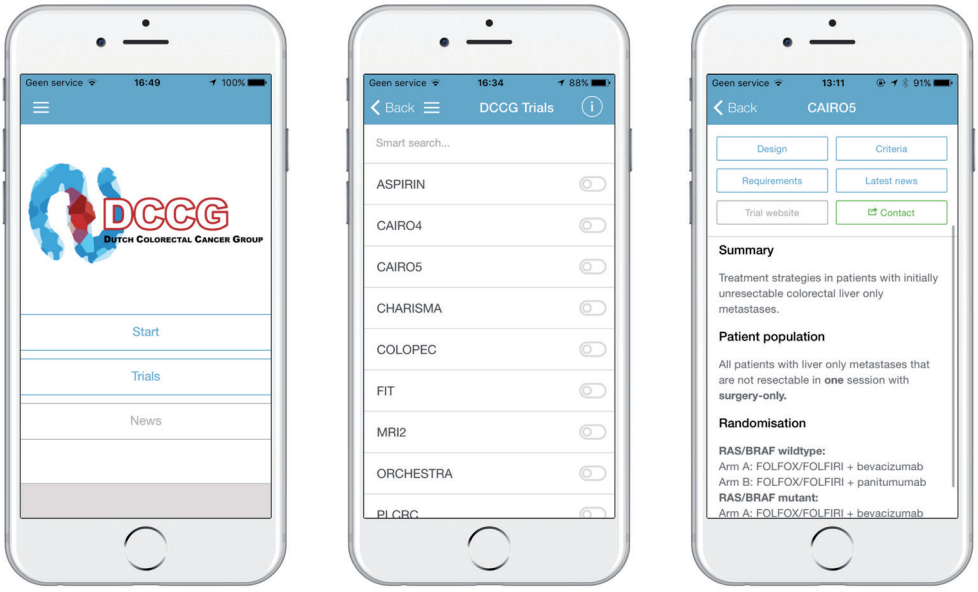

Figure 2. Illustration of the home screen, trials overview and a trial information page

Respondents were working either in a teaching (40%), or academic hospital (32%), or general hospital (19%), 9% of the responders defined their working place as 'other'. Eighty-three percent of all respondents rated the application 4 or higher for satisfaction on a 5-point scale, and 86% recommended the application to a colleague. Highest reported reasons of use were: urgent trial inquiry (57%) and usage during multi-disciplinary meetings (49%).

Figure 3. Overview of the reasons for application use. 75 out of 121 people answered this question.

Reason	N (%)
When I have a (urgent) question about a specific DCCG trial	43 (57%)
During multi-disciplinary meetings	37 (49%)
During my work at the outpatient clinic	23 (31%)
In preparation for the outpatient clinic	20 (27%)
In preparation for multi-disciplinary meetings	18 (24%)
When I finished work, mostly in the evening or at home	8 (11%)
Other	6 (8%)

DISCUSSION

The present study illustrates that a smartphone application with concise information on multi-center trials on colorectal carcinoma is often used and reported satisfaction with the app is high. More than 70% of the users are medical doctors or nurses and the application is mostly used during multi-disciplinary meetings and work at the outpatient clinic. The DCCG Trials application is an experimental tool that provides concise information on clinical trials which might benefit patient inclusion. This application could offer insights for implementation in other clinical fields.

Since the DCCG is based in the Netherlands, it was to be expected that most users derive from the Netherlands. The increased Dutch user duration rate supports the suggestion that the application is a useful tool when professionals are confronted with potential inclusions. The survey illustrated a majority of the users were physicians in teaching hospitals. [14] Compared to academic centers, these hospitals often have a higher patient turnover but lower awareness of ongoing trials, which could be a potential cause of slow patient enrollment. The application directly offers information on in- and exclusion criteria, increasing the chances of patient inclusion. Additionally, patient inclusion often has a certain momentum in clinical practice. If eligibility can directly be assessed by use of the application or when a potential trial candidate can directly be discussed with the trial coordinator, likelihood of patient enrollment increases. Lastly, the option to directly update users with new trial information, reminds users of the existence of a trial, indirectly increasing the likelihood of including patients in trials.

This is the first study presenting data of an application with the goal to improve clinical trial conduction and patient recruitment. Many applications have been developed in which trial information can be found. [15-18] However, no data is available about the effect of these applications on the conduction and recruitment of clinical trials. Little evidence is available for any intervention on the effect of patient recruitment in clinical trials. [10] It is difficult to prove the effect of the Dutch Colorectal Cancer Group Trials app on trial enrollment. However, the fact that the application is frequently used by relevant users suggest that an

application with relevant information on ongoing trials could have a positive effect on trial enrollment.

The current analyses have several limitations. Firstly, presenting data on the duration of sessions and trial page visits does not necessarily reflect a positive user experience or positive effect on the conduction of a particular trial. Preferably the effect of the application on inclusion rates is investigated but the available data and trials was limited and a direct causal effect of the application on inclusion rates would be difficult to assess. Secondly, the survey was made available online, and respondents were recruited though the app, DCCG newsletter, and DCCG mailing list, which could have introduced selection bias. It can be assumed that users that are very positive about the application are more willing to submit a survey, yet it could also be assumed that users with a very negative user experience are motivated to express their opinion.

In conclusion, we report that our smartphone application with study information of ongoing colorectal cancer trials is frequently used and the majority of users is satisfied. The application provides easy to access and up to date information on ongoing clinical trials and could be useful for medical professionals in their busy daily practices. These results warrant the development of an application including all registered clinical trials in which users can select their own trials of interest, including all diseases and specialties.

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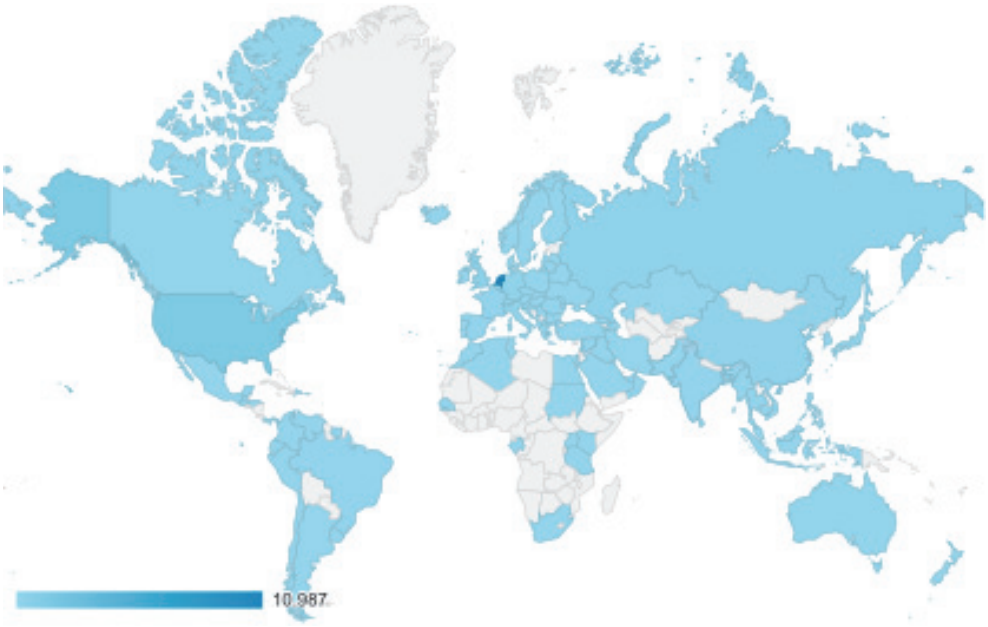
18 Resource LOCT., http://www.Emergingmed.Com/support/lilly.Html.

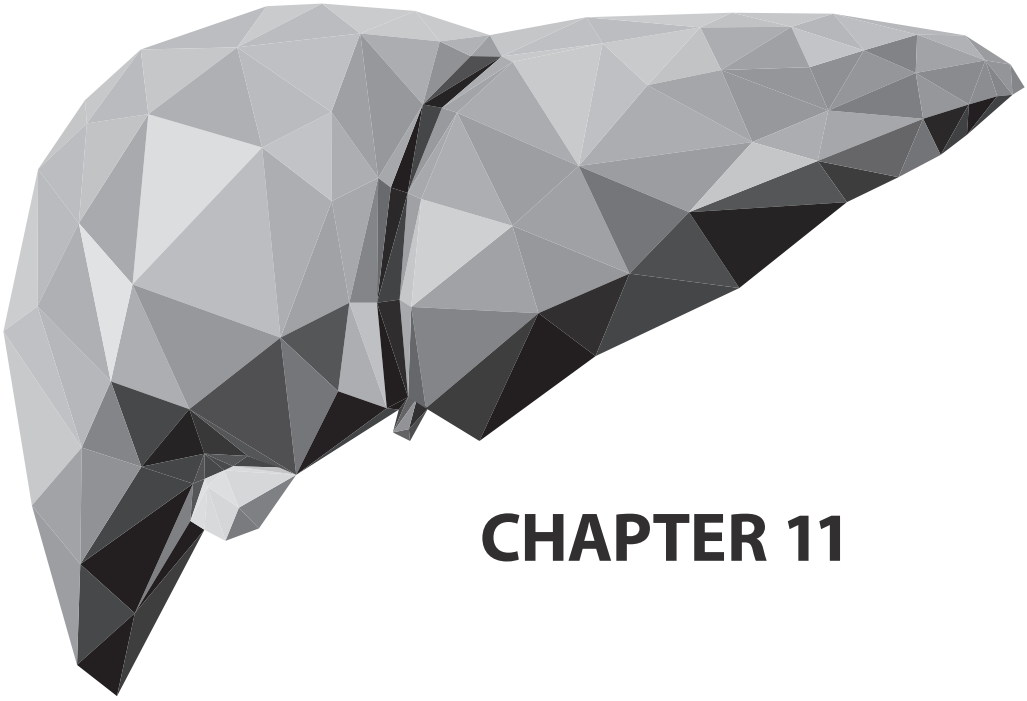
Appendix 1. An overview of the conducted survey

Questions	Answer
1 Do you use the DCCG Trials App? *	*Yes / No*
2 Why don't you use the DCCG Trials App?	*Free text*
3 What is your profession?	*Medical doctor* *(Research) Nurse* *Researcher* *Data manager* *Other*
4 What is your age?	*N (years)*
5 In what type of institution do you work?	*Academic hospital* *Teaching hospital (STZ ziekenhuis)* *General hospital* *Other*
6 Are you satisfied with the DCCG Trials App	*Score: 1-5 (Strongly disagree - Strongly agree)*
7 Do you agree with the following statement: I would recommend the DCCG Trials App to my colleagues.	*Score: 1-5 (Strongly disagree - Strongly agree)*
8 When do you use the DCCG Trials App? *(multiple answers possible)*	*During multi-disciplinary meetings.* *In preparation for multi-disciplinary meetings.* *During my work at the outpatient clinic.* *In preparation for the outpatient clinic.* *When I finished work, mostly in the evening or at home.* *When I have a (urgent) question about a specific DCCG trial.* *Other*
9 For how long have you used the DCCG Trials App?	*N (months)*
10 What is your average session duration when you use the DCCG Trials App?	*<2 minutes* *2-5 minutes* *>5 minutes*
11 Do you have any feedback that you would like to share?	*Free text*

*If answer is 'No' only question 2 and 11 could be submitted, if answer is 'Yes' question 2 could not be submitted



Supplementary figure 1. Overview of all the countries in which the application has been used



CHAPTER 11

Risk of bias assessment in an age of open-access scientific literature

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** contributed equally*

Submitted

ABSTRACT

Background

Scientific publications are becoming increasingly more accessible to a greater public. Assessment of risk of bias is a key element in the interpretation of the reliability of the results of clinical research. This study aimed to assess the agreement of risk of bias assessment of a randomized controlled study (RCT) between individuals with limited scientific experience and the reference standard defined as a team of Cochrane reviewers.

Methods

During 2016-2017, four cohorts (C1, C2, C3, C4) of sixth year medical students assessed the risk of bias of one out of three RCTs of different levels of risk of bias (R1, R2, R3). Their interpretation was compared with the assessment provided in Cochrane reviews.

Results

In total, 256 students (C1=145, C2=61, C3=50) participated. Overall, the answers of students were in 61% (8%-97%) consistent with those of the Cochrane review. High consistency was found for the item random sequence generation (90%), followed by moderate consistency for blinding of participants (71%), incomplete outcome data assessment (69%), blinding of outcome assessors (64%), and allocation concealment (63%). Blinding of personnel (43%) and selective outcome reporting (31%) showed poor consistency.

Conclusion

Risk of bias assessment of RCTs can be a challenge for individuals lacking scientific experience. The consistency of risk of bias assessment between inexperienced individuals and Cochrane reviewers varied from 31% to 90% per topic, illustrating a potential pitfall for the interpretation of scientific articles and applicability of their results. The increasing amount of open-access available scientific articles demands for methodologic aid instruments in order to emancipate readers with limited scientific experience.

INTRODUCTION

The declaration of Helsinki (1964) is a fundamental document stating modern human research ethics and obligates to publish clinical trial information and results.[1] Since then, both politicians and public institutions have been making efforts to ensure a growing number of scientific articles being made available to a wider 'laymen' public, also referred to as open-access.[2] However, since the results of research heavily depend on its methodological quality, providing clinicians and patients access to scientific information might not be sufficient to make well-informed shared decision.

In current medical practice, most of the information on the effectiveness of treatments comes from randomized controlled trials (RCT) as they are still considered to be the golden standard.[3] A RCT of poor methodological quality may produce unreliable results with potentially harmful consequences when implemented in a clinical setting.[4] In order to use the information coming from trials, it is essential to assess the potential risk of bias and the certainty of the results . Therefore, this is considered as one of the evidence-based medicine core competencies for healthcare professionals. However, it requires skills and time to extensively read an article.[5]

One of the solutions in order to tackle this problem, systematic reviews (SR) and meta-analyses (MA) were introduced as a way to structurally assess and summarize the quality of the evidence of the exponentially growing number of randomized controlled trials.[6] In 2008, Cochrane has developed a Risk of Bias assessment tool (Cochrane RoB) that is currently internationally widely used in SRs and MAs.[7] Unfortunately, such overview articles with guidance on how to interpret the results and certainty of the evidence only appear after a significant amount of studies on a particular topic have been executed and published.

As medical information gets increasingly more accessible, laymen with limited scientific experience should be able to assess the methodological quality of studies when interpreting their results. It might be so that current methodological assessment tools are ill suited for a less experienced public. As a consequence, laymen (e.g. science journalists, family members of patients) might attribute an incorrect value to scientific results. It was the aim of this study to assess the consistency of risk of bias assessment between individuals with limited scientific experience and experienced Cochrane review author teams.

METHODS

Students

All sixth-year medical students at the University of Utrecht, The Netherlands, were included during September 2016-May 2017. They were divided in three groups (C1, C2, C3). Informed consent to participate was obtained through the risk of bias assignment as mentioned

below. It was mandatory for the students to do the assignment. The students didn't receive any grade for the assignment and didn't follow formal training on how to assess the methodological quality of a trial yet.

Randomized Controlled Trials

The search for RCTs to be assessed was performed via the following steps. First, a topic of interest was identified by the authors JH and EB. Second, a search term was stated in the Cochrane Library. If a Cochrane review with risk of bias assessment on this topic was available, this review was selected. Third, a RCT of this review was randomly selected by drawing straws. These actions were performed on three different topics resulting in three different RCTs.

Risk of Bias Assignment

An online English questionnaire was constructed using Typeform.[8] The full questionnaire is available in Supplementary Table 1. The questionnaire consisted of a set of questions concerning the study's baseline characteristics, the content of the trial and lastly a set concerning risk of bias assessment. RoB assessment consisted of seven topics which were defined according to the Cochrane Handbook[9]: random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome data, incomplete outcome data and selective reporting. Each component was accompanied by its brief explanation from the Cochrane Handbook. Students had to choose between 'high risk', 'unclear risk' and 'low risk'. For each student cohort, the choice with the largest majority within the group regarding risk reflected the group result. To support judgements of risk of bias assessment, two phrases from the article had to be cited for each topic. Consent to use anonymised data was obtained through the questionnaire.

Statistical Analysis

Data were gathered and descriptive statistics were performed using SPSS version 23.0. Consistency was defined as the percentage overlap between student choices and the assessments of the Cochrane review author teams.

RESULTS

Students

During a period from September 2016 to May 2017, 256 students participated. All students gave permission to use their assessment for research purposes. The total group had an average age of 24 (IQR 23-25) years. The majority (N=226, 88%) had no experience with the use of the Cochrane risk of bias assessment tool. Cohort 1 (C1) assessing RCT 1 consisted of

Table 1. Student Characteristics

Students		**N (%)**
	Total	256 (100)
	C1- RCT 1	145 (57)
	C2- RCT 2	61 (24)
	C3- RCT 3	50 (19)
Age	(median, IQR)	24 (23-25)
Used ROB prior to assessment		**N (%)**
	Never	226 (88)
	1-3 Times	27 (11)
	>3 Times	3 (1)

Table 2. Cochrane risk of bias assessment - Number of students that agreed with Cochrane assessment

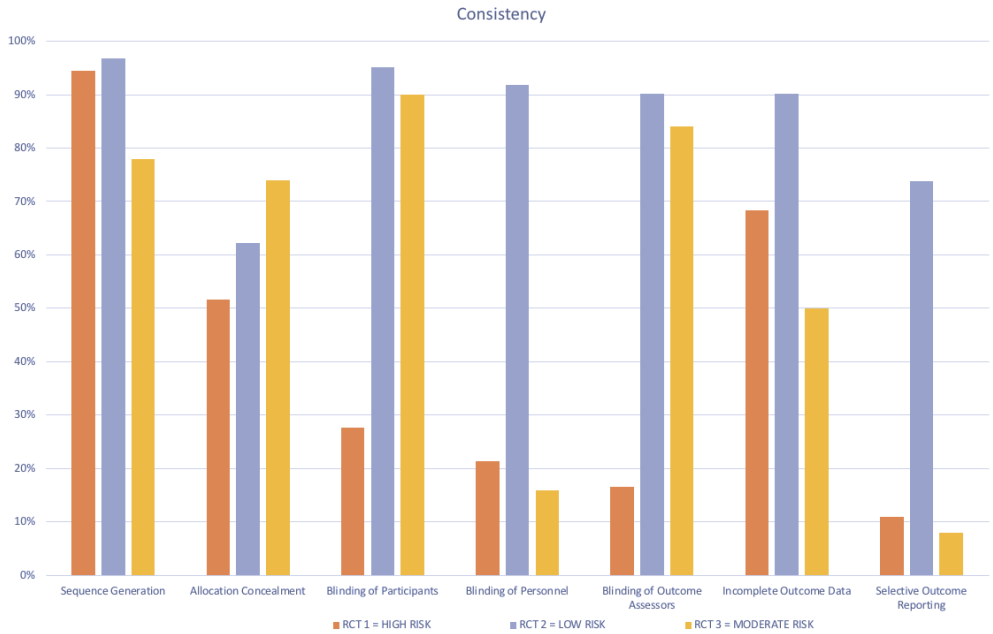
		Cochrane risk assessment						
		Random Sequence Generation	**Allocation Concealment**	**Blinding of Participants**	**Blinding of Personnel**	**Blinding of outcome assessment**	**Incomplete Outcome Data**	**Selective Reporting**
1	Gill 2011	+	+	+	-	-	+	-
	Students (n=145)	137 (94%)	75 (52%)	40 (28%)	31 (21%)	24 (17%)	99 (68%)	16 (11%)
2	Ruiz Tovar 2015	+	+	+	+	+	+	+
	Students (n=61)	59 (97%)	38 (62%)	58 (95%)	56 (92%)	55 (90%)	55 (90%)	45 (74%)
3	Kovacic 2013	+	+	-	-	+	?	+
	Students (n=50)	39 (78%)	37 (74%)	87 (34%)	43 (17%)	42 (84%)	73 (28%)	37 (74%)

+ low risk of bias ? moderate risk of bias - high risk of bias consistency < 30%

145 students, Cohort 2 (C2) assessing RCT 2 of 61 students and Cohort 3 (C3) of 50 students. A summary is described in Table 1.

Randomized Controlled Trials

The included RCTs were respectively Gill 2011 (R1)[10], Ruiz-Tovar 2015 (R2)[11] and Kovacic 2013 (R3)[12]. Gill et al.[10] investigated different methods of visualization techniques for laparoscopic surgery. Ruiz Tovar et al.[11] performed a trial investigating dressing methods after colorectal surgery. Lastly, Kovacic et al.[12] examined the impact of relaxation training after breast cancer surgery. The Cochrane risk of bias assessment of all studies are described in Table 2.



Risk of Bias Topic		RCT 1 (N=145)	RCT 2 (N=61)	RCT 3 (N=50)
Overall	**N (%)**	60 (42)	52 (86)	29 (57)
Sequence Generation	**N (%)**	137 (95)	59 (97)	39 (78)
Allocation Concealment	**N (%)**	75 (52)	38 (62)	37 (74)
Blinding of Participants	**N (%)**	40 (28)	58 (95)	8 (16)
Blinding of Personnel	**N (%)**	31 (21)	56 (92)	8 (16)
Blinding of Outcome Assessors	**N (%)**	24 (17)	55 (90)	42 (84)
Incomplete Outcome Data	**N (%)**	99 (68)	55 (90)	25 (50)
Selective Reporting	**N (%)**	16 (11)	45 (74)	4(8)

Figure 1. Consistency between students and Cochrane reviewers per topic

Risk of Bias Assessment

All 256 students fully completed the assessment. In all three RCTs, components that were regarded as 'low risk' by the Cochrane reviewers, were regarded similarly by more than 50% of the students (range 52%-97%). On components rated by reviewers as 'unclear risk', only 28% of the students agreed. If Cochrane reviewers interpreted components as 'high risk', students often disagreed (11%-34%).

Consistency

For each topic of risk of bias assessment, absolute agreement of the interpretation by the students and the Cochrane reviewers was assessed. These results are summarized in

Figure 1. High consistency was found for the item random sequence generation (90%), followed by moderate consistency for blinding of participants (71%), incomplete outcome data assessment (69%), blinding of outcome assessors (64%), and allocation concealment (63%). Blinding of personnel (43%) and selective outcome reporting (31%) showed poor consistency.

DISCUSSION

The consistency of risk of bias assessment between inexperienced individuals and Cochrane reviewers varies from 31% to 90% per topic, illustrating a potential pitfall for methodological interpretation of scientific articles. Well-defined, unambiguous criteria such as 'random sequence generation' and 'blinding of participants' show greater agreement compared to complex components such as 'selective outcome reporting'. To our knowledge, this is the first study evaluating the knowledge of risk of bias assessment by individuals with limited scientific experience.

The components of the risk of bias tool were chosen based on empirical evidence demonstrating their association with effect estimates.[13] However, if the reader of an article lacks the ability to adequately assess these components, their value is limited. The results of this study illustrate these difficulties in particular when several elements of a study have a high risk of bias. This might potentially lead to an underestimation of poorly executed studies. Laymen often search for scientific articles that support a therapy that they are inclined to prefer (e.g. a family member of a terminal cancer patient in search for last resort therapies). It is possible that laymen are more at risk to neglect poor methodological quality and therefore will focus solely on the results.[14]

The current study shows that the rapidly growing group of lay readers faces difficulties with risk of bias assessment as well. Previous studies have shown that even the interrater reliability of experienced individuals assessing studies with this risk of bias tool, is low.[15,16] Savovic et al. in 2014[17] showed a similar trend stating that the standardized approach of the risk of bias tool was an advantage, but that the component 'selective reporting of outcomes' was difficult to interpret. These results might suggest that a constructive discussion towards a more unambiguous risk of bias tool would be useful.

This study has some limitations that should be considered in the interpretation of its results. A limited number of trials was assessed. This approach was chosen deliberately to represent laymen searching for evidence. The student groups were not equal in size due to. However, since attendance was obligatory, the risk of selection bias remains limited.

The description of methodology in prosaic sentences can lead to ambiguous interpretation and has even proven to be a potential disguise of fraudulent research.[18] There might be a danger of underestimating the risk of bias of studies as students appear

to experience more difficulties with the interpretation of studies with low methodologic quality. As in other fields of science (e.g. computer programming, mathematics), the introduction of symbols or standardized phrases could potentially limit these risks.[19] There is a need for transparency of the complete process of development, conduct and publishing of medical research in which methodological assessment plays a major role.

In the coming years, the number of scientific publications will continue to grow exponentially, making it difficult for methodological expertise centres such as Cochrane to assess all studies in time.[20] Publication of a systematic review or a meta-analysis can take several years after the publication of the original RCTs. Leading journals could potentially develop open-access risk assessments for laymen to assess a study's methodological quality at the moment of publication of the original trial. This will reveal potential high risk studies earlier and will increase the transparent aspect of science as a whole.

CONCLUSION

In conclusion, risk of bias assessment of randomized controlled trials can be a challenge for individuals lacking scientific experience. Structured reporting of risk of bias assessment and open-access display of the results could potentially diminish interpretation variability in less experienced clinicians and others interested in the results of scientific publications, So that in the end, scientific results can really become open-access.

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Supplementary Figure 1. Risk of Bias Assignment

1 Intake

a. First name *

b. Last name *

Date of birth (dd-mm-yyyy) *

dd/mm/yyyy

c. Student number *

d. E-mail address *

e. How often have used risk of bias assessment? *

- Never
- 1-3 Times
- >3 Times

3 Risk of Bias Assessment Article: Image inversion and digital mirror-image technology aid laparoscopic surgery task performance in the paradoxical view:a randomized controlled trial (Gill 2010)

In case you don't have a copy of the article anymore, you can view and download it here.

https://www.dropbox.com/s/01h1v32087kfz19/Gill%202010.pdf?dl=0

a. What type of research is this article? *

- ○ Cohort study
- ○ Systematic review
- ○ Meta-analysis
- ○ Randomized controlled trial

b. How many participants were included? *

c. In how many groups were the study participants divided? *

d. Describe the intervention in group 1 (max 2 sentences). *

e. Describe the intervention in group 2 (max 2 sentences). *

f. What primary outcome was measured?

g. Random sequence generation (selection bias*) *

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence

There is a **low risk of selection bias** if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).

There is a **high risk of selection bias** if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention

○ low risk ○ high risk ○ unclear risk

h. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

i. Allocation concealment (selection bias) *

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

There is a **low risk of bias** if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes.

There is a **high risk of bias** if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures

○ low risk ○ high risk ○ unclear risk

j. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

k. Blinding of participants *

Performance bias due to knowledge of the allocated interventions by participants during the study

There is a **low risk of bias** if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

○ low risk ○ high risk ○ unclear risk

l. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

m. Blinding of personnel/care providers (perfomance bias) *

Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study.

There is a **low risk of performance bias** if blinding of personnel was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

○ low risk ○ high risk ○ unclear risk

n. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

o. Blinding of outcome assessment (detection bias) *

Detection bias due to knowledge of the allocated interventions by outcome assessors

There is **low risk of detection bias** if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding

○ low risk ○ high risk ○ unclear risk

p. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

q. Incomplete outcome data addressed (attrition bias) *

Attrition bias due to amount, nature or handling of incomplete outcome data.

There is a **low risk of attrition bias** if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data were balanced in numbers, with similar reasons for missing data across groups**; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardized difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size, or missing data were imputed using appropriate methods. (Note: if dropouts are very large, imputation using even "acceptable" methods may still suggest a high risk of bias)

○ low risk ○ high risk ○ unclear risk

r. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

s. Selective reporting (reporting bias) *

Reporting bias due to selective outcome reporting

There is **low risk of reporting bias** if the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way, or if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

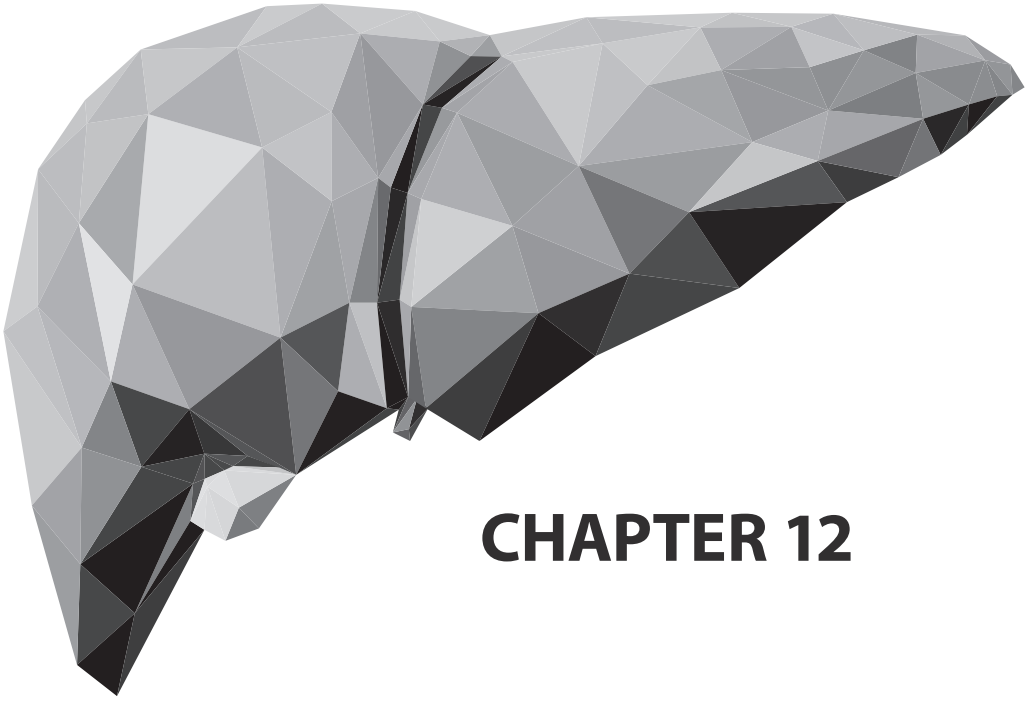
There is a **high risk of reporting bias** if not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study

○ low risk ○ high risk ○ unclear risk

t. Cite the phrases from the article that support your judgement as conscise as possible (max 2 sentences). *

Submit

IN CONCLUSION



CHAPTER 12

Summary and discussion

This thesis is subdivided in two parts. **Part 1** deals with the challenges to select the optimal treatment for patient's colorectal liver metastases. **Part 2** describes the challenges of the conduction of clinical research and offers possible technologies to improve the conduction of clinical research. In this chapter, the results of this thesis are summarized and discussed.

PART 1

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide.[1] Most cancer deaths are the result of progression of metastases.

Resection of colorectal liver metastases (CRLM) offers the chance of long-term disease-free survival or cure, with 5-year survival rates of resection ranging between 25% and 58%.[2–4] Colorectal cancer patients with unresectable liver-only metastases may be cured after downsizing of metastases by neoadjuvant systemic therapy. However, the optimal neoadjuvant induction regimen has not been defined, and the lack of consensus on criteria for (un)resectability complicates the interpretation of published results. Decision making on optimal treatment strategy in patients with initially unresectable colorectal cancer liver metastases (CRLM) remains complex because uniform criteria for (un)resectability are lacking.

Chapter 1 describes the protocol of the multicenter, randomized, phase 3 clinical trial CAIRO5. Colorectal cancer patients with initially unresectable liver-only metastases are eligible. The (un)resectability status is prospectively assessed by a central panel consisting of at least one radiologist and three liver surgeons, according to predefined criteria. Tumours of included patients will be tested for *RAS* and *BRAF* mutation status and primary tumor location will be defined. Patients with *RAS* and *BRAF* wild type and left-sided colorectal tumours will be treated with doublet chemotherapy (FOLFOX or FOLFIRI) and randomized between the addition of either bevacizumab or panitumumab, and patients with *RAS* or *BRAF* mutant and/or right-sided primary colon tumours will be randomized between doublet chemotherapy (FOLFOX or FOLFIRI) plus bevacizumab or triple chemotherapy (FOLFOXIRI) plus bevacizumab. Radiological evaluation to assess conversion to resectability will be performed by the central panel, at an interval of two months.

The primary study endpoint is median progression-free survival. Secondary endpoints are the R0/1 resection rate, median overall survival, response rate, toxicity, pathological response of resected lesions, postoperative morbidity, and correlation of baseline and follow-up evaluation with respect to outcomes by the central panel. The unique aspects of CAIRO5 concern the prospective phase 3 randomised comparison of neoadjuvant treatment regimens in this population with the use of uniform and transparent criteria for

unresectability by an expert panel. This CAIRO5 panel may contribute to a consensus on criteria for unresectability and to awareness of secondary resections in these patients.

Chapter 2 demonstrates a successful implementation and feasibility of the CAIRO5 national DCCG Liver Expert Panel in clinical practice. The median time to panel conclusion of 7 days was considerably faster than the preconceived maximum of 14 days allowing efficient assessment by multiple experienced liver surgeons in these very complex patients. Despite resectability assessments by a panel of experienced liver surgeons, a high level of inter-surgeon disagreement per assessment was observed, as shown in earlier studies.[5–8] This underlines the complexity of defining (un)resectability and supports the evaluation of CRLM patients by a panel of liver surgeons rather than by an individual surgeon or MDT in order to achieve a more reproducible and more balanced decision per patient.

Portal vein embolization

Postoperative liver failure is a severe complication after liver resection and is the most important cause of death after liver surgery.[9,10] Since, the incidence of postoperative liver failure is directly related to the volume of the future liver remnant (FLR),[11–14] liver surgery is only considered safe if the FLR consists of at least 20-30% of the total liver volume.[15] Preoperative portal vein embolization (PVE) is a technique in which one side of the portal venous system is occluded to induce hypertrophy of the contralateral liver lobe. PVE is currently considered the golden standard to preoperatively increase the FLR when it's volume is less than 20-30% in order to decrease the risk of liver failure.[16,17] There is an ongoing controversy surrounding PVE regarding the short-term safety of PVE and long-term oncological benefit. In **Chapter 3** we retrospectively analysed a group of 745 patients from four liver centres in The Netherlands who underwent major liver surgery, of whom 53 underwent preoperative PVE. Patients who underwent PVE had more extensive disease in terms of number and diameter of liver metastases and more often had synchronous disease, which results in a bias towards direct comparison with non-PVE patients. After propensity score matching, PVE patients were compared to a similar cohort of non-PVE patients and had similar disease-free and overall survival. The clinical relevance of tumour progression remains a subject of debate. Progressive metastases are commonly located in the part of the liver that will be resected. These patients are thought to have a worse outcome after resection compared to patients without progression after PVE. This study shows that patients who underwent major liver resection after PVE have similar outcomes compared to patients without PVE. The relevance of tumour progression in these patients might be limited and several reports have likely been biased by the higher tumor load in the PVE patients compared to non-PVE patients. Although postoperative complications were higher in patients who underwent pre-operative PVE, it remains a valuable tool to increase resectability rate of patients with CRLM.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)

ALPPS induces extensive and rapid liver regeneration and allows the resection of colorectal liver metastases (CRLM) with curative intent which would otherwise be unresectable and only eligible for palliative systemic therapy. However, the oncological outcomes of CRLM patients following ALPPS are uncertain.[18–21] The oncological value of ALPPS for advanced colorectal liver metastases (CRLM) was analyzed in **chapter 4**. Overall survival following ALPPS in patients with advanced colorectal liver metastases was not superior to matched patients that received palliative systemic therapy. The disease-free survival following ALPPS is limited when compared to other surgical strategies. The reduced DFS after ALPPS compared to standard two stage procedures suggest that the detection of progression has shifted from the inter-stage interval to the postoperative period following stage 2 of ALPPS. The short interval (median 11 days) between stage one and two of ALPPS most likely does not allow sufficient time for detection of disease progression. Almost all patients are subjected to both stages including its morbidity and mortality. It remains a question whether ALPSS is a reasonable option in the treatment of advanced CRLM, considering the modern systemic treatment options available today. Careful selection of patients for ALPPS and non-surgical options is advised along with adequate patient counseling, taking into account the reported increased mortality rate and uncertain oncological outcomes.

Chapter 5 presents two separate risk scores that were generated in order to predict the risk of mortality following stage-1 or 2 of ALPPS using variables available before the respective stage in order to allow risk assessment. Both risk scores achieved fair predictive value with AUC values above 0.70, and allow adequate stratification of CRLM patients into low, intermediate, and high-risk subgroups. The analyses showed that a considerable proportion of patients (11%) with CRLM undergo ALPPS without neoadjuvant chemotherapy. This practice raises questions since ALPPS patients should be considered to have initially non-resectable liver metastases and would therefore be candidates for systemic therapy in the context of a conversion strategy.

The current risk score includes only CRLM patients and did not exclude any patient based on total center-volume but rather used total center-volume and experience as variables in the analyses. The CRLM risk-score demonstrates that older patients with small remnant livers in inexperienced centers, especially after experiencing morbidity after stage-1 have adverse outcomes. With this risk score CRLM patients can be stratified to low, intermediate, or high risk for ALPPS and may be used to limit ALPPS to low-risk CRLM patients.

Hepatic vascular inflow occlusion (VIO) can be applied during resection of CRLM to control intra-operative blood loss but has been linked to accelerated growth of micro metastases in experimental models.[22–24] In **Chapter 6** the results that identify intermittent VIO with severe ischemia during resection of CRLM as independent predictor of reduced DFS without affecting OS are presented. It remains unclear what the clinical impact of these finding is especially considering intraoperative blood transfusion is also related with OS

in multivariate analysis. The benefits of applying VIO during resection must outweigh the oncological risks besides other risks such as impaired remnant liver function. This requires a patient tailored approach.

PART 2

Prospective randomised trials such as the CAIRO5 trial are considered to be the golden standard to test the effectiveness of medical interventions and are therefore at the core of 'evidence-based' healthcare. This research typically involves a large number of patients, and therefore the participation of multiple centres. The initiation and conduct of these multicentre studies require a significant investment of patients, healthcare professionals and other stakeholders. The Netherlands have an excellent track record of clinical research which is considered due to a well organised research infrastructure in which academic and general hospitals are actively participating.[25] **Part 2** of this thesis presents the results of the performance of the conduction of clinical research and of new technologies and approaches to improve and facilitate the conduction of clinical research.

Central medical ethical approval and subsequent local approval of the participating centres for feasibility are required before a trial can be initiated. The increasing complexity and diversity of the procedure to obtain approval for local feasibility causes delay and increases costs.[26–31] **Chapter 7** demonstrates a large variety in time, content and costs of the procedures for obtaining approval for local feasibility of participating centres concerning two Dutch multicentre studies. These variations are unpredictable and pose a serious obstacle in conducting scientific clinical research in The Netherlands. Delay in the process of initiation of studies decrease the chance of successful accrual of patients and thereby endanger their successful completion. This is not acceptable from the perspective of patients, researchers and funding bodies. Collaboration with all stakeholders on further standardization, centralization and digitalization of the procedure would be of great value.

Chapter 8 presents the results of a study in which publication rates, timely dissemination of results and the prevalence of consistency in hypothesis, sample size and primary endpoint of Dutch investigator-initiated randomized controlled clinical trials. A publication rate of 77% among 168 Dutch investigator-initiated RCT within 5 years after the completion of patient accrual of the RCT was observed. Median time to publication was 30 months (IQR 19-43) and only 30% (50/168) of the results were published within two years after the completion date. A low overall consistency in hypothesis, sample size calculation and primary endpoint was found, with only 39% of the 129 published RCTs being consistent in all three parameters. The observed publication rate of Dutch investigator-initiated RCT is higher than earlier reports.[32–39] However, in this study we found that approximately one out of four Dutch RCT remains unpublished after five years. Investigators of these unpublished

RCT were planning to recruit a total of 8850 patients. Although the actual number of accrued patients in these unpublished RCT is unknown, a significant number of patients will have been exposed to experimental treatments without any attribution to clinical science. Moreover, the observed low overall consistency is a continuous matter of concern.[34,40] Results of a RCT with discrepancy in hypothesis, sample size calculation or primary endpoint might be unreliable and biased. Publication rates and consistency should be frequently studied to improve the conduction and reporting of RCTs. New IT solutions could be used to facilitate the conduction and monitoring of clinical research.

Chapter 9 illustrates that a smartphone application with concise information on multi-center trials on colorectal carcinoma is often used. Reported satisfaction with the app is high. More than 70% of the users are medical doctors or nurses and the application is mostly used during multi-disciplinary meetings and work at the outpatient clinic. The DCCG Trials application is an experimental tool that provides concise information on clinical trials which might benefit patient inclusion. Little evidence is available for any intervention on the effect of patient recruitment in clinical trials.[41] It is difficult to prove the effect of the Dutch Colorectal Cancer Group Trials app on trial enrollment. However, the fact that the application is frequently used by relevant users suggest that an application with relevant information on ongoing trials could have a positive effect on trial enrollment. These results warrant the development of an application including all registered clinical trials in which users can select their own trials of interest, including all diseases and specialties.

Chapter 10 demonstrates that the consistency of risk of bias assessment between inexperienced individuals and Cochrane reviewers varies from 31% to 90% per topic, illustrating a potential pitfall for methodological interpretation of scientific articles. Well-defined, unambiguous criteria such as 'random sequence generation' and 'blinding of participants' show greater agreement compared to complex components such as 'selective outcome reporting'. The current study shows that the rapidly growing group of lay readers faces difficulties with risk of bias assessment. Previous studies have shown that even the interrater reliability of experienced individuals assessing studies with this risk of bias tool, is low.[42,43] These results might suggest that a constructive discussion towards a more unambiguous risk of bias tool would be useful. Leading journals could potentially develop open-access risk assessments for laymen to assess a study's methodological quality at the moment of publication of the original trial. This could reveal potential high-risk studies earlier and will increase the transparent aspect of science as a whole.

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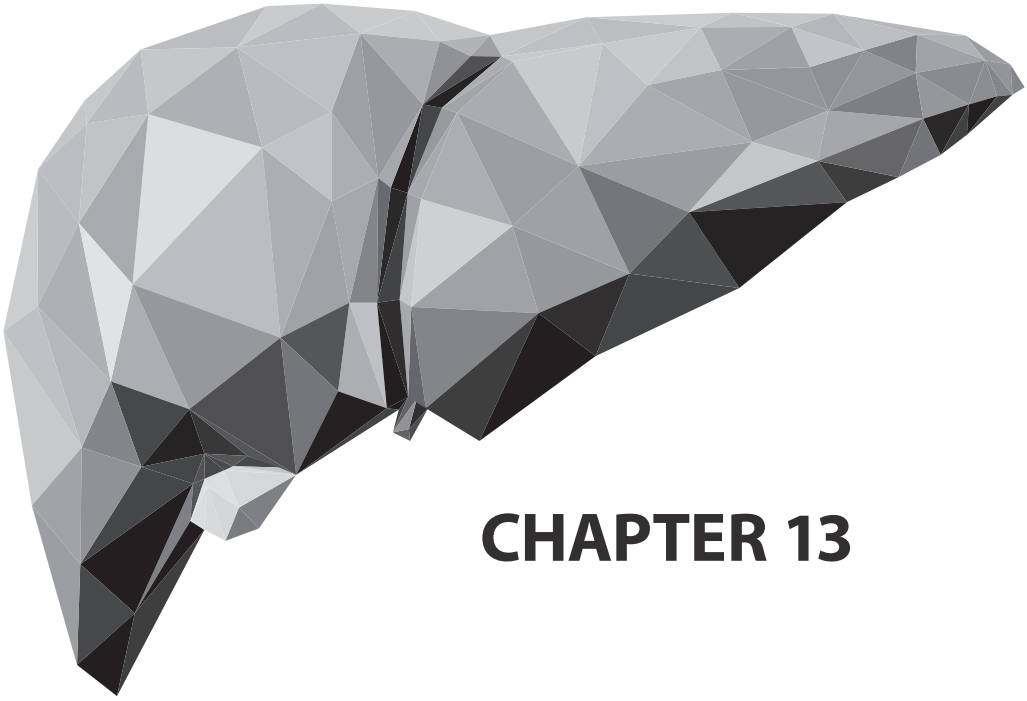


CHAPTER 13

Nederlandse Samenvatting

Dit proefschrift is onderverdeeld in twee delen. **Deel 1** gaat over de uitdagingen om de optimale behandeling te selecteren voor patiënten met colorectale levermetastasen. **Deel 2** beschrijft de uitdagingen van de uitvoering van klinisch onderzoek en beschrijft mogelijke technologieën om de uitvoering van klinisch onderzoek te verbeteren. In dit hoofdstuk worden de resultaten van dit proefschrift samengevat en besproken.

DEEL 1

Colorectaal carcinoom is de derde meest voorkomende kanker en de tweede doodsoorzaak door kanker wereldwijd. De meeste sterfgevallen door kanker zijn het gevolg van progressie van metastasen.

Resectie van colorectale levermetastasen (CRLM) biedt de beste kans op langdurige ziektevrije overleving of zelfs genezing. Na resectie van CRLM varieert de 5-jaars overleving tussen 25% en 58%. Patiënten met irresectable CRLM kunnen alsnog genezen worden na een goede volume afname door neoadjuvante systemische therapie. Het optimale neoadjuvante inductie regime is echter niet bekend en het gebrek aan consensus over criteria voor resectabiliteit bemoeilijkt de interpretatie van gepubliceerde resultaten. Besluitvorming over optimale behandelstrategie bij patiënten met aanvankelijk niet-resecteerbare CRLM blijft vanwege het ontbreken van uniforme criteria voor resectabiliteit complex.

Hoofdstuk 1 beschrijft het protocol van de multicenter, gerandomiseerde, fase 3 klinische studie CAIRO5. Patiënten met aanvankelijk niet-resecteerbare uitzaaiingen van colorectaal carcinoom naar alleen de lever komen in aanmerking voor de studie. De resectabiliteit status wordt prospectief beoordeeld door een centraal panel bestaande uit ten minste één radioloog en drie leverchirurgen volgens vooraf gedefinieerde criteria. Tumoren van geïncludeerde patiënten worden getest op RAS- en BRAF-mutatiestatus en de primaire tumorlocatie wordt gedefinieerd. Patiënten met RAS en BRAF wildtype en linkszijdige colorectale tumoren worden behandeld met doublet chemotherapie (FOLFOX of FOLFIRI) en gerandomiseerd tussen de toevoeging van ofwel bevacizumab of panitumumab, en patiënten met RAS of BRAF mutant en/ of rechtszijdige primaire dikke darmtumoren worden gerandomiseerd tussen doublet chemotherapie (FOLFOX of FOLFIRI) plus bevacizumab of drievoudige chemotherapie (FOLFOXIRI) plus bevacizumab. Radiologische evaluatie om de conversie naar resecteerbaarheid te beoordelen wordt door het centrale panel uitgevoerd met een interval van twee maanden.

Het primaire eindpunt van de studie is mediane progressievrije overleving. Secundaire eindpunten zijn de R0/1 resectiegraad, mediane totale overleving, respons, toxiciteit, pathologische respons van gereseceerde laesies, postoperatieve morbiditeit en correlatie

van baseline en follow-upevaluatie met betrekking tot de resultaten door het centrale panel. De unieke aspecten van CAIRO5 betreffen de prospectieve gerandomiseerde fase 3-vergelijking van neoadjuvante behandelingsregimes in deze populatie met het gebruik van uniforme en transparante criteria voor resectabiliteit door een expert panel. Dit CAIRO5-panel kan bijdragen aan een consensus over criteria voor resectabiliteit en aan het bewustzijn voor secundaire resecties bij deze patiënten.

Hoofdstuk 2 toont een succesvolle implementatie en haalbaarheid van het nationale DCCG Lever Expert Panel in de klinische praktijk. De mediane tijd tot een panelconclusie van 7 dagen is aanzienlijk sneller dan het vooropgestelde maximum van 14 dagen, waardoor een efficiënte beoordeling door meerdere ervaren leverchirurgen bij deze zeer complexe patiënten mogelijk is. Ondanks dat de resectabiliteit werd beoordeeld door een panel van ervaren leverchirurgen, is er, zoals ook aangetoond is in eerdere studies, een hoog aantal van inter-chirurgische meningsverschillen per beoordeling waargenomen. Dit onderstreept de complexiteit van het definiëren van resectabiliteit en ondersteunt het evalueren van CRLM-patiënten door een panel van leverchirurgen in plaats van door een individuele chirurg of een multidisciplinair team om een meer reproduceerbare en meer evenwichtige beslissing per patiënt te bereiken.

Vena porta embolisatie

Postoperatief leverfalen is een ernstige complicatie na leverresectie en is de belangrijkste doodsoorzaak na een leveroperatie. De incidentie van postoperatief leverfalen is direct gerelateerd aan het volume van de toekomstige rest lever (TRL). Leverchirurgie wordt daarom alleen veilig beschouwd als de TRL bestaat uit ten minste 20-30% van het totale levervolume. Preoperatieve vena porta embolisatie (VPE) is een techniek waarbij één kant van het porta veneuze systeem wordt afgesloten om hypertrofie van de contralaterale leverkwab te bewerkstelligen. VPE wordt momenteel beschouwd als de gouden standaard om het volume van de TRL preoperatief te verhogen om het risico op leverfalen te verminderen wanneer dit volume minder dan 20-30% is. Er is een controverse over de veiligheid op de korte termijn van VPE en over het oncologisch voordeel van VPE op de lange termijn. **Hoofdstuk 3** beschrijft een retrospectieve analyse van een groep van 745 patiënten uit vier levercentra in Nederland die een grote leveroperatie ondergingen en waarvan 53 patiënten preoperatief VPE ondergingen. Patiënten die VPE ondergingen, hadden een uitgebreidere ziekte in termen van aantal en diameter van levermetastasen en hadden vaker synchrone ziekte. Dit resulteert in een bias bij een directe vergelijking met niet-VPE-patiënten. Na propensity score matching werden VPE-patiënten vergeleken met een vergelijkbaar cohort van niet-VPE-patiënten en hadden VPE-patiënten een vergelijkbare ziektevrije en algehele overleving. De klinische relevantie van tumorprogressie na VPE blijft onderwerp van discussie. Progressieve metastasen bevinden zich meestal in het deel van de lever dat zal worden verwijderd. Men denkt dat deze patiënten een slechtere uitkomst hebben na

resectie in vergelijking met patiënten zonder progressie na VPE. Deze studie toont aan dat patiënten die na VPE een grote leverresectie ondergingen vergelijkbare resultaten hebben als patiënten zonder VPE. De relevantie van tumorprogressie bij VPE-patiënten kan beperkt zijn en in verschillende studies is waarschijnlijk een bias geïntroduceerd door uitgebreidere ziekte bij de VPE-patiënten in vergelijking met niet-VPE-patiënten. Hoewel postoperatieve complicaties hoger waren bij patiënten die preoperatief VPE ondergingen, blijft VPE een waardevol hulpmiddel om de resectabiliteit van patiënten met CRLM te verhogen.

Gelijktijdige levertranssectie met vena portae ligatie tijdens een leverresectie in twee fasen (ALPPS) induceert uitgebreide en snelle leverregeneratie. ALPSS maakt de resectie van CRLM van patiënten mogelijk die anders niet reseceerbaar zouden zijn en alleen in aanmerking kwamen voor palliatieve systemische therapie. De oncologische resultaten van CRLM-patiënten na ALPPS zijn echter onzeker. De oncologische waarde van ALPPS voor geavanceerde CRLM werd geanalyseerd in **hoofdstuk 4**. De totale overleving na ALPPS bij patiënten met geavanceerde CRLM was niet superieur aan gematchte patiënten die behandeld werden met palliatieve systemische therapie. De ziektevrije overleving na ALPPS is beperkt in vergelijking met andere chirurgische strategieën. De verminderde ziektevrije overleving na ALPPS in vergelijking met standaard "two-stage" procedures suggereert dat de detectie van progressie is verschoven van het interval tussen twee resecties in naar de postoperatieve periode na fase 2 van ALPPS. Het korte interval (mediaan 11 dagen) tussen stadium één en twee van ALPPS biedt hoogstwaarschijnlijk onvoldoende tijd voor detectie van ziekteprogressie. Bijna alle patiënten ondergaan beide stadia, inclusief morbiditeit en mortaliteit. Het blijft de vraag of ALPSS een redelijke optie is bij de behandeling van geavanceerde CRLM, gezien de moderne systemische behandelingsopties die vandaag beschikbaar zijn. Zorgvuldige selectie van patiënten voor ALPPS en niet-chirurgische opties wordt geadviseerd samen met adequate counseling van de patiënt, rekening houdend met het gerapporteerde verhoogde sterftecijfer en onzekere oncologische resultaten.

Hoofdstuk 5 presenteert twee afzonderlijke risicoscores die werden gegenereerd om het risico op sterfte na fase 1 of 2 van ALPPS te voorspellen met behulp van variabelen die vóór de betreffende fase beschikbaar waren. Beide risicoscores bereikten een redelijke voorspellende waarde met AUC-waarden boven 0,70. De risicoscores maken een adequate stratificatie van CRLM-patiënten in subgroepen met een laag, gemiddeld en hoog risico mogelijk. Uit de analyses bleek dat een aanzienlijk deel van de patiënten (11%) met CRLM ALPPS ondergaat zonder neoadjuvante chemotherapie. Deze praktijk roept vragen op, aangezien ALPPS-patiënten in eerste instantie als niet-resectabele levermetastasen moeten worden beschouwd en daarom in aanmerking komen voor systemische therapie in de context van een conversiestrategie.

De huidige risicoscore omvat alleen CRLM-patiënten en sluit geen enkele patiënt uit op basis van het aantal operaties van een centrum. De CRLM-risicoscore toont aan dat oudere patiënten met een kleine restlever in onervaren centra, vooral na het ervaren van morbiditeit

na stadium 1, negatieve uitkomsten hebben. Met deze risicoscore kunnen CRLM-patiënten worden gestratificeerd naar een laag, gemiddeld of hoog risico voor ALPPS en kunnen ze worden gebruikt om ALPPS te beperken tot CRLM-patiënten met een laag risico.

The Pringle manoeuvre waarbij de afferente hepatische vasculatuur wordt geoccludeerd (VIO) om perioperatief bloedverlies te limiteren kan worden toegepast tijdens resectie van CRLM. In experimentele modellen is VIO in verband gebracht met versnelde groei van micrometastasen. In **hoofdstuk 6** worden de resultaten gepresenteerd waarbij intermitterende VIO met ernstige ischemie tijdens resectie van CRLM geïdentificeerd wordt als onafhankelijke voorspeller van verminderde ziektevrije overleving zonder de totale overleving te beïnvloeden. Het blijft onduidelijk wat de klinische impact van deze bevinding is, vooral gezien het feit dat perioperatieve bloedtransfusie ook verband houdt met totale overleving in een multivariate analyse. De voordelen van het toepassen van VIO tijdens resectie moeten opwegen tegen de oncologische risico's en andere risico's zoals verminderde leverfunctie. Dit vereist een patiëntgerichte aanpak.

DEEL 2

Prospectief gerandomiseerde studies zoals de CAIRO5-studie worden beschouwd als de gouden standaard om de effectiviteit van medische interventies te toetsen en vormen daarom de kern van 'evidence-based' gezondheidszorg. Bij dit type onderzoek is meestal een groot aantal patiënten betrokken en daarom ook de deelname van meerdere centra. Voor het initiëren en uitvoeren van deze multicentrische onderzoeken is een aanzienlijke investering van patiënten, professionals in de gezondheidszorg en andere belanghebbenden vereist. Mede door een goed georganiseerde onderzoek infrastructuur, waaraan academische en algemene ziekenhuizen actief deelnemen, heeft Nederland een uitstekende staat van dienst op het gebied van klinisch onderzoek. **Deel 2** van dit proefschrift presenteert de resultaten van onderzoek naar de uitvoering van klinisch onderzoek en van nieuwe technologieën en benaderingen om de uitvoering van klinisch onderzoek te verbeteren.

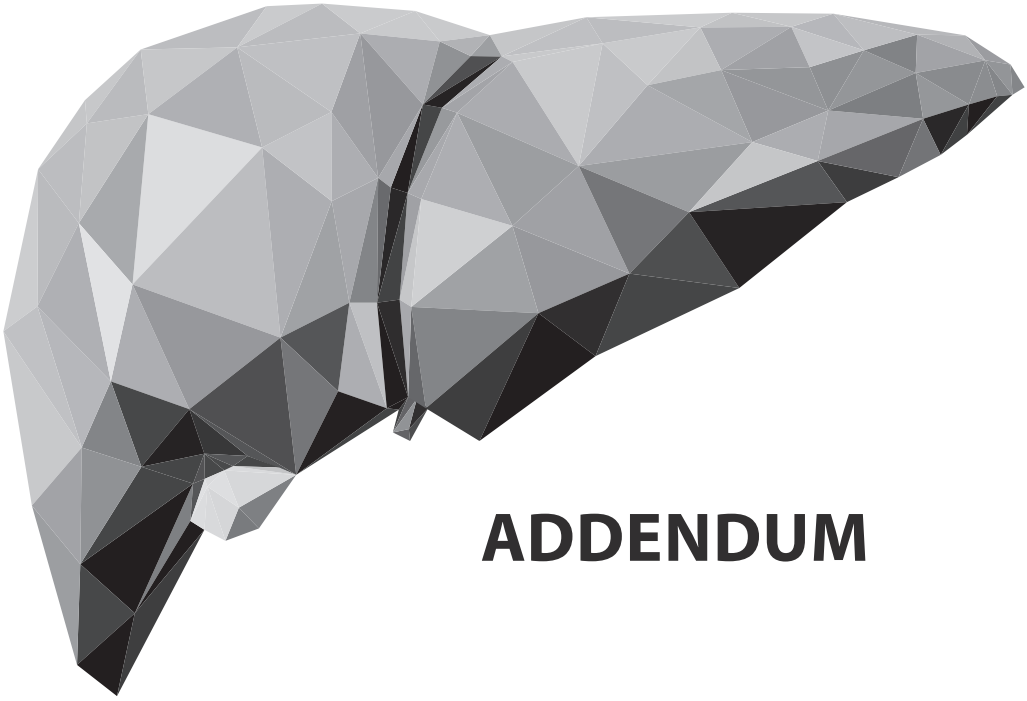
Centrale medische ethische goedkeuring en daaropvolgende lokale goedkeuring van de deelnemende centra voor haalbaarheid zijn vereist voordat een klinische studie met patiënten kan worden gestart. De toenemende complexiteit en diversiteit van de procedure voor het verkrijgen van goedkeuring voor lokale haalbaarheid veroorzaakt vertraging van onderzoek en verhoogt de kosten. **Hoofdstuk 7** toont een grote variatie in tijd, inhoud en kosten van de procedures voor het verkrijgen van goedkeuring voor lokale haalbaarheid van deelnemende centra aan twee Nederlandse multicenter studies. Deze variaties zijn onvoorspelbaar en vormen een ernstig obstakel bij het uitvoeren van wetenschappelijk klinisch onderzoek in Nederland. Vertraging in het proces van het initiëren van studies vermindert de kans op succesvolle rekrutering van patiënten en brengt

daarmee een succesvolle voltooiing van een studie in gevaar. Dit is niet acceptabel vanuit het perspectief van patiënten, onderzoekers en financieringsinstanties. Samenwerking tussen alle belanghebbenden bij verdere standaardisatie, centralisatie en digitalisering van de procedure zou van grote waarde zijn.

Hoofdstuk 8 presenteert de resultaten van een onderzoek waarin publicatiepercentages, tijdige verspreiding van resultaten en de prevalentie van consistentie in hypothese, steekproef omvang en het primaire eindpunt van Nederlandse onderzoeker geïnitieerde randomized controlled trials (RCT). Er werd een publicatiepercentage van 77% binnen 5 jaar na sluiten van de studie waargenomen onder 168 Nederlandse onderzoeker geïnitieerde RCTs. De mediane tijd tot publicatie was 30 maanden (IQR 19-43) en slechts 30% (50/168) van de resultaten werd binnen twee jaar na de voltooiingsdatum gepubliceerd. Er werd een lage algemene consistentie in hypothese, steekproef omvang en primair eindpunt gevonden, waarbij slechts 39% van de 129 gepubliceerde RCTs consistent was in alle drie de parameters. Het waargenomen publicatiepercentage in deze studie is hoger dan eerdere gerapporteerde resultaten. In dit onderzoek hebben we echter vastgesteld dat ongeveer een op de vier Nederlandse RCT na vijf jaar nog niet is gepubliceerd. Onderzoekers van deze niet-gepubliceerde RCTs waren van plan in totaal 8850 patiënten te werven. Hoewel het werkelijke aantal geïncludeerd patiënten in deze niet-gepubliceerde RCTs onbekend is, is het goed mogelijk dat een aanzienlijk aantal patiënten is blootgesteld aan experimentele behandelingen zonder dat dit geleid heeft tot een bijdrage de klinische wetenschap. Bovendien is de waargenomen lage algehele consistentie een punt van zorg. Resultaten van een RCT met discrepantie in hypothese, steekproef omvang of primair eindpunt kunnen onbetrouwbaar en bevooroordeeld zijn. Publicatiepercentages en consistentie moeten regelmatig worden bestudeerd om de uitvoering en rapportage van RCTs te verbeteren. Nieuwe IT-oplossingen kunnen worden gebruikt om de uitvoering en monitoring van klinisch onderzoek te vergemakkelijken en verbeteren.

Hoofdstuk 9 laat zien dat een smartphone applicatie met beknopte informatie over multicenter onderzoek naar colorectaal carcinoom vaak wordt gebruikt. De gerapporteerde tevredenheid over de app is hoog. Meer dan 70% van de gebruikers zijn artsen of verpleegkundigen. De applicatie wordt meestal gebruikt tijdens het multidisciplinair overleg en op de polikliniek. De DCCG Trials-applicatie is een experimenteel hulpmiddel dat beknopte informatie biedt over lopende klinische onderzoeken. De applicatie zou de inclusie van patiënten ten goede kunnen komen. Er is weinig bewijs beschikbaar over welke interventie een effect hebben op de inclusie van patiënten in klinisch onderzoek. Het effect van de DCCG Trials-applicatie op de inclusie is moeilijk aan te tonen. Het feit dat de applicatie vaak door relevante gebruikers wordt gebruikt, suggereert echter dat een applicatie met relevante informatie over lopende onderzoeken een positief effect kan hebben op de inclusie. Deze resultaten rechtvaardigen de ontwikkeling van een applicatie waarin alle geregistreerde klinische studie staan en gebruikers voor hen relevante studies kunnen selecteren.

Hoofdstuk 10 laat zien dat de consistentie van een risico op bias-beoordeling tussen onervaren personen en Cochrane-beoordelaars varieert van 31% tot 90% per onderwerp. Dit illustreert een mogelijke valkuil voor methodologische interpretatie van wetenschappelijke artikelen. Goed gedefinieerde, ondubbelzinnige criteria zoals 'random sequence generation' en 'blindering van deelnemers' tonen meer overeenstemming in vergelijking met meer complexe componenten zoals 'selectieve uitkomstrapportage'. Deze studie toont aan dat de snelgroeiende groep leken lezers problemen heeft met het inschatten van risico op bias. Deze resultaten zouden kunnen suggereren dat een constructieve discussie over een meer eenduidige risico op bias-tool nuttig zou kunnen zijn. Toonaangevende tijdschriften kunnen mogelijk open-access risicobeoordelingen ontwikkelen voor leken om de methodologische kwaliteit van een studie te beoordelen op het moment van publicatie. Dit zou in een eerder stadium "risico" studies kunnen identificeren en zou transparantie van de wetenschap kunnen verhogen.



ADDENDUM

List of Publications

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PhD portfolio

Name PhD student: Joost Huiskens PhD period: March 2014-June 2017 Name PhD supervisor: prof. dr. C.J.A. Punt, prof.dr. T.M. van Gulik		
1. PhD training		
	Year	**Workload (Hours/ ECTS)**
General courses BROK (Basiscursus regelgeving en Organisatie voor Klinisch onderzoekers)	2015	1.0
Specific courses Clinical Epidemiology 1: Randomized Clinical Trials	2015	0.9
Presentations Viable tumor tissue adherent to needle applicators after local ablation: a risk factor for local tumor progression. SEOHS Rotterdam, Nederland	2010	0.5
Viable tumor tissue adherent to needle applicators after local ablation: a risk factor for local tumor progression. EAHBPA Kaapstad, Zuid-Africa	2011	0.5
Logistic and ethical aspects of the Dutch nationwide colorectal liver metastases expert panel. EAHPBA Manchester, Engeland	2015	0.5
TrialApp: an application to lower the barrier for patient participation in clinical research. Personalized medicine & health research, Amersfoort, Nederland	2015	0.5
Inter-observer variability of resectability assessment of colorectal liver metastases: preliminary results of the Dutch colorectal cancer group (DCCG) liver metastases expert panel. IHBPA Sao Paolo, Brazilië	2016	0.5
Challenges in clinical research. Dutch Clinical Research Foundation, Woerden Nederland	2016	0.5
Healthcare, research and technology *In search of the optimal love triangle.* ClinOpsDag, Veenendaal, Nederland	2017	0.5
Portal vein embolization prior to resection of colorectal liver metastases does not impact oncological outcomes. E-AHPBA Mainz, Duitsland	2017	0.5
Evaluatie van colorectale levermetastasen: eerste resultaten van het CAIRO5 colorectale lever metastase expert panel van de Dutch Colorectal Cancer Group (DCCG). Chirurgendagen Veldhoven, Nederland	2017	0.5
Challenges in Healthcare, Research and data technology - Cancer Center Amsterdam. SAS Global Forum Nieuwegein, Nederland	2017	0.5

	Year	Workload (Hours/ ECTS)
(Inter)national conferences		
SEOHS Rotterdam, Nederland	2010	0.5
EAHPBA, Kaapstad, Zuid-Africa	2011	0.75
EAHPBA, Manchester, United Kingdom	2015	0.75
IHBPA, Sao Paolo, Brazilië	2016	0.75
Chirurgendagen 2015, Veldhoven, the Netherlands	2015	0.5
Chirurgendagen 2016, Veldhoven, the Netherlands	2016	0.5
Chirurgendagen 2017, Veldhoven, the Netherlands	2017	0.5
ClinOpsDag, Veenendaal, Nederland	2017	0.5
Other		
Lead developer DCCG trials app	2015	2
Lead developer TrialApp	2016	2
Lead developer NVGIC Trials Dashboard	2017	2
Lead developer Porsch Trial App	2017	2
Lead developer Nederlands Trial Register	2017	2
Guest Editor Journal of Clinical and Translational Research	2017	2
Clinical lead of the Cancer Center Amsterdam & SAS collaboration on improvement of selection of CRLM patients through advanced analytics	2016	3
Orginisation of the Symposium of the 52nd International Meeting of the European Society for Surgical Research (ESSR)	2017	0.5
2. Teaching		
Supervising		
Masterthesis Medicine Student	2016	1.5
Masterthesis Medicine Student	2017	1.5
Bachelor Thesis Medicine Student	2016	1.5
3. Parameters of Esteem		
Grants		
Stichting Kwaliteitsgelden Medisch Specialisten	2015	

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Beste Martijn jij hebt me geholpen structuur te brengen in de chaos. Jij motiveerde mij een artikel te schrijven over de DCCG app. De gesprekken bij jou op kamer hielpen mij de lijnen uit te zetten. Heel erg bedankt!

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Beste Karen, jij hebt de CAIRO5 overgenomen en samen hebben we het panel paper geschreven. Ik ben blij dat we het nog steeds zo goed met elkaar kunnen vinden. Ik wens je heel veel succes bij de verdere coördinatie van de studie en jouw promotie.

Het IKNL-team: Astrid Keijzer, Jonne Schriek en Baukje Hemmes
Beste Astrid. Wij hebben zo intensief samengewerkt! Zonder jou was het landelijk panel

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LAB genoten
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Lieve Anne, mijn beste maatje en liefste vrouw. Zonder jouw steun, begrip en onvoorwaardelijke liefde was mij dit nooit gelukt.

Curriculum Vitae

Joost Huiskens was born on October 29th 1983 in Rotterdam, the Netherlands.

Joost graduated at the Erasmiaans Gymnasium in Rotterdam. He studied medicine at the University of Amsterdam. After obtaining his medical degree, Joost worked as a resident (ANIOS) for 1 year at the department of surgery at the Albert Schweizer Hospital in Dordrecht (dr. P.W. Plaisier) and for 1 year at the department of surgery at the Academic Medical Center Amsterdam (prof. dr. O.R.C. Busch). He then took the opportunity to start his research in the field of hepatobiliary surgery and medical oncology at the Academic Medical Center in Amsterdam under supervision of prof. dr. T.M. van Gulik and prof. dr. C.J.A. Punt. During his PhD training, he was coordinator of the multi center randomized phase 3 trial CAIRO5 and he studied the treatment strategies for patients with colorectal liver metastases.

During his research Joost developed multiple applications to support the conduct of clinical research. Joost also initiated the CAESAR-project on biomedical image analysis and advanced analytics to improve outcomes in patients with colorectal liver metastases.

After working for six months at the Erasmus Medical Center, Joost started working in the healthcare team of SAS Netherlands. At SAS Joost focuses on all challenges to implement analytics in healthcare.

Joost is the proud husband of Anne Josephina Maria van der Eerden and father of Tomas, Isa and Johanna Huiskens.