

# **Conservative treatment versus elective repair of umbilical hernia in patients with liver cirrhosis and ascites: A study protocol**

B. de Goede  
H.H. Eker  
W.C.J. Hop  
M. de Boer  
W.G. Polak  
P. Taimr  
R.A. de Man  
J.F. Lange  
H.J. Metselaar  
G. Kazemier

## ABSTRACT

*Background:* The optimal management of patients with umbilical hernia and liver cirrhosis is not clear. The general surgical opinion is that umbilical hernia in patients with liver cirrhosis and ascites should not be corrected, because of the presumed high operative risks and high recurrence rates after elective repair. Conservative treatment, however, can also have severe complications resulting in emergency repair. In these patients such operations carry an even greater risk of complications than compared to elective operations. To date, no randomized controlled trial has been conducted on this subject.

*Methods/Design:* our trial is a multi-center, randomized controlled trial designed to compare watchful waiting to elective repair of umbilical hernia in patients with liver cirrhosis and ascites. The primary endpoint consists of a composite endpoint of overall morbidity related to the treatment of umbilical hernia after 24 months of follow-up. Secondary endpoints will include: cumulative hernia recurrence rate, classification of complications obtained during follow-up, postoperative pain and quality of life. A total of 100 patients will be randomized between the two groups. Patients will visit the outpatient clinic at 2-3 weeks and after 3, 12 and 24 months of follow-up.

*Conclusion:* This study will provide level 1b evidence to support the preference for either conservative treatment or elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

*Trial registration:* Clinicaltrials.gov: NCT01421550

## INTRODUCTION

Patients with liver cirrhosis complicated with ascites have a 20% risk of developing an umbilical hernia in the course of their disease.<sup>1</sup> Possible factors that contribute to the development of umbilical hernia in these patients include increased intra-abdominal pressure due to ascites, weakening of the abdominal fascia and muscle wasting as a result of a poor nutritional status, and dilatation of the umbilical vein that enlarges the preexistent supra-umbilical fascial opening in patients with portal hypertension.<sup>2</sup>

Optimal management of an umbilical hernia in patients with liver cirrhosis remains controversial. It is often advised that surgical correction of an umbilical hernia in patients with ascites should not be performed before liver transplantation. In those patients a “wait-and-see” approach is recommended, because of the presumed increased surgical risks and high recurrence rates after elective repair.<sup>3-5</sup> Conservative treatment, however, can be complicated by incarceration or spontaneous rupture and evisceration following necrosis of the overlying skin. This requires an emergency repair which puts patients at greater risk of complications – even greater than after elective repair.<sup>6-8</sup> If a patient is a candidate for liver transplantation and repair has not been performed prior to transplantation, umbilical hernia correction should be performed during liver transplantation because of the reported risk of postoperative strangulation of the bowel in uncorrected umbilical hernia resulting in serious morbidity and death.<sup>8</sup>

One specific group of patients still warrants conservative treatment of umbilical hernia or repair only during liver transplantation: patients with a patent umbilical vein. A reopened umbilical vein can be an important route of outflow for the portal circulation in patients with severe portal hypertension. In these patients, elective repair without liver transplantation has been reported to result in acute portal vein thrombosis and subsequent liver failure necessitating an emergency liver transplantation because of ligation of the umbilical vein during hernia repair.<sup>2,7,9</sup>

Because of all these increased risks, liver cirrhosis, particularly in the presence of portal hypertension was initially considered an absolute contraindication for elective umbilical hernia repair. Despite this widespread belief, some small retrospective and prospective series have shown good results with elective umbilical hernia repair for patients with liver cirrhosis.<sup>6-8</sup> However, no randomized controlled trial on this issue has been published.

The CRUCIAL trial was designed to determine the optimal management of umbilical hernia in patients with liver cirrhosis and ascites.

## Objective

The objective of the CRUCIAL trial is to compare conservative treatment (watchful waiting) to elective repair of umbilical hernia in patients with liver cirrhosis and ascites. We hypothesize that elective repair of umbilical hernia will result in a significant reduction of overall complication rate and improved quality of life compared to conservative treatment in patients with liver cirrhosis and ascites.

Primary endpoint will be a composite endpoint of the overall morbidity related to the treatment of umbilical hernia after 24 months of follow-up. Secondary endpoints include cumulative hernia recurrence rate, classification of complications obtained during follow-up, and assessment of pain and quality of life.

## METHODS AND STUDY DESIGN

### Study design

The CRUCIAL trial has been designed as a prospective, multi-center, randomized controlled trial, in which conservative treatment is compared to elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

The design of this protocol is in accordance with the CONSORT guideline.<sup>10</sup> Approval of the Medical Ethical Committee Erasmus MC, Rotterdam, The Netherlands, was obtained. In total a 100 patients will be included in this study. Patients will be randomized in one of two groups of 50 patients each. Group 1 includes patients with liver cirrhosis and ascites that will undergo elective umbilical hernia repair; group 2 includes patients with cirrhosis and ascites that will receive conservative treatment with regard to their umbilical hernia.

Randomization will be done in the Erasmus Medical Center for each participating center. Patients are randomly allocated to either conservative treatment or elective repair by means of sealed, numbered envelopes and will be opened in sequence. The randomization procedure will be stratified for participating center and for Model of End-stage Liver Disease (MELD) score  $\leq 15$  and  $> 15$ . Blinding for the allocation is not possible in this study for the study participants, evaluators and surgeons.

Patients will visit the outpatient clinic after 2-3 weeks and after 3, 12 and 24 months. At 12 months of follow-up ultrasound imaging will be performed to detect recurrent umbilical hernia. All patients will be asked to fill out the Short-Form 36 (SF-36) and EuroQol (EQ-5D) to assess quality of life and a Visual Analogue Scale (VAS) to assess pain preoperatively and during follow-up.

## Participants

All patients with liver cirrhosis and ascites who have a concurrent umbilical hernia will be assessed for eligibility. Informed consent is mandatory. Before eligible patients can be included, ultrasound imaging will be performed to determine the size of the umbilical hernia and the presence of a patent umbilical vein. If the umbilical vein is either closed or open, but the diameter doesn't exceeds 5 mm, the patient is permitted to participate in the CRUCIAL trial.

Umbilical hernia repair will also be performed in patients who are allocated to conservative treatment group and develop a symptomatic umbilical hernia during follow-up. Simultaneous umbilical hernia repair will be performed if a patient will undergo abdominal surgery or a liver transplantation before the umbilical hernia correction is performed as stated in the flowchart (Fig. 1).

Inclusion criteria are defined as follows:

- § Primary umbilical hernia
- § Liver cirrhosis
- § Ascites (proven or treated)
- § Age  $\geq$  18 years
- § Signed Informed consent

Exclusion criteria:

- § Recurrent umbilical hernia
- § Midline laparotomy in the medical history
- § ASA (American Society of Anaesthesiologists) score IV or above
- § Incarcerated umbilical hernia necessitating an emergency procedure
- § The presence of a patent umbilical vein larger than 5mm
- § Expected time to liver transplantation more than 3 months

## Interventions

### Preoperative work-up

Elective repair of the umbilical hernia will be performed within 8 weeks after the randomization procedure. Prior to the randomization procedure, ultrasound imaging will be performed to determine the presence of a patent umbilical vein. Patients who undergo elective repair of the umbilical hernia will be admitted to the hospital two days prior to the procedure. The presence of tense ascites (i.e. more than 5 liters) will be treated with diuretic therapy or with drainage, and if necessary, albumin levels will be corrected until  $> 30$  g/L.

### Intra-operative procedure

All repairs of the umbilical hernia, either elective repair or emergency surgery after conservative treatment, will take place using a method for which consensus is reached by all participating centers. This includes a para-umbilical incision, dissection (avoiding resection) of the hernia sac and restoration of the sac and its contents into the abdominal cavity. Intra-operative resection of the sac must be recorded on the patient's operation report. Repair should take place using non-absorbable monofilament sutures combined with a flat polypropylene mesh placed preferably in the on-lay position or in the pre-peritoneal plane.<sup>11</sup> The overlap achieved in repair should be at least 3 cm's in each direction of the circular mesh. Closure of the subcutaneous tissue and skin may be achieved using a method chosen by the individual surgeon. If a patient with liver cirrhosis and concurrent umbilical hernia will undergo liver transplantation during follow up, repair should also take place using preferably non-absorbable monofilament sutures combined with a flat polypropylene mesh placed in the on-lay position or in the pre-peritoneal plane.

The preferred method of anaesthesia in the current trial is general anaesthesia. The use of local or spinal anaesthesia is permitted if there are contra-indications for general anaesthesia. Single dose Kefzol® (Cefazoline) should be administered as antibiotic prophylaxis 10 to 30 minutes preoperatively. Furthermore, routine administration of thrombosis prophylaxis should be considered in the form of bodyweight adjusted Low Molecular Weight Heparin.

Case record form (intra-operative procedure) asks for completion of all fields noted, such as technical details of procedure (incision, size of the defect and the use of mesh and drains), duration of procedure, complications during procedure, thrombosis prophylaxis, intravenous antibiotics and method used for anaesthesia.

In mesh hernia repair the umbilical defect should not be enlarged during the repair procedure. If the surgeon sees need to enlarge the umbilical defect during the operation (which is not the preferred procedure) the enlargement of the defect must be noted in the operation report. The surgeon is permitted to close the fascia defect using sutures if possible in a “tension free fashion” to protect the mesh from contact with umbilical skin. In order to protect the viscera it is possible to place omentum or the remains of the hernia sac between viscera and mesh. The use of drains is permitted. Closure of the subcutaneous tissue and skin may be achieved using a method chosen by the individual surgeon.

### **Peri-operative management of clotting disorders**

Without signs of bleeding complications, prolonged prothrombin time (PT) or a platelet count below 30 should not be corrected.<sup>12</sup> If necessary, for instance in bleeding complications, correct PT/INR with low-volume coagulation factor concentrates, like co-factor®. Preferably not with FFP's because of a fluid overload side effect, potentially leading to more bleeding complications because of a rise venous pressure.<sup>13</sup>

### **Postoperative procedure**

Post-operative analgesics may consist of tramadol 50 mg three times daily and paracetamol four times daily 500 mg (or equivalent) administered orally for six days after surgery. Surgical wounds are examined for signs of haematoma and seroma. Albumine levels should be >30 g/L before the patient is allowed to return home. Diuretics controls and post-operative care will be performed at the outpatient clinic of the department of Hepatology. Postoperative care will be in close collaboration with a specialized hepatologist and concordant with good standard of care for operated patients with liver cirrhosis.

### **Outcome measures**

Primary endpoint in this study is a composite endpoint of the overall morbidity (percentage of patients with at least one hernia-related complication) after 24 months of follow-up. Overall morbidity, which is divided in minor and major complications, can be found in Table 1.

Secondary endpoints are: cumulative recurrence of umbilical hernia after repair in the separate groups, and grading of the primary endpoint (overall morbidity) with use of the Landelijke Heelkundige Complicatie Registratie (LHCR) grading tool; per patient the maximal observed grade will be determined and compared between the two groups. Pain will be evaluated with VAS and quality of life will be evaluated with SF-36 and EQ-5D questionnaires.

All complications defined in Table 1, both conservative treatment and elective repair, will be scored with the LHCR for grading complications in surgical patients (Table 2). The following surgical procedures will not be scored as complications: liver transplantation, elective or emergency repair of the umbilical hernia. In each patient the maximal observed grade will be determined and compared between the two groups.

**Table 1.** *Minor and major complications.*

<i>Minor complication</i>	<i>Major complication</i>
Superficial/deep SSI	Mortality
Seroma	Evisceration
Pneumonia	Strangulation
Haematoma	Incarceration
Urinary tract infection	Bowel ischemia
Non-closure of surgical wound at 4 weeks	Necrosis/rupture of the overlying skin of the umbilical hernia
	Postoperative leakage of ascites more than 2 weeks after surgery
	Liver failure
	Infectious ascites
	Decompensated cirrhosis
	Organ space SSI
	Unexpected ICU admissions related to umbilical hernia or umbilical hernia repair

**Table 2.** *The Landelijke Heelkundige Complicatie Registratie (LHCR) grading tool.*

<i>Grade</i>	<i>Description of complications</i>
0	No health disadvantage, no real complication
1	Temporary health disadvantage, recovery without (re) operation
2	Recovery after (re) operation
3	(likely) permanent damage or invalidity
4	Death

## Sample size calculation

Group sizes are based on chi-square tests with  $\alpha = 0.05$ , a power of 90% and are based on an expected decrease in overall complication rate at 2-years from 50 to 15% due to elective umbilical hernia repair.<sup>8</sup> This requires 42 patients per treatment group. Accounting for approximately 15% dropout during the trial and 5% lost to follow-up, a total of 50 patients per group need to be recruited.

### Statistical analysis

Hundred patients with an umbilical hernia will be included in the study. Patients will be randomized in one of two groups of 50 patients each stratified by center and MELD  $\leq 15$  and  $>15$ . Data will be analyzed on an “intention to treat” basis.

Categorical variables will be presented as numbers (percentage). Continuous variables will be presented as medians (range). Categorical variables will be compared using the Chi-square test. Continuous variables will be compared using the Mann-Whitney U test.

Kaplan-Meier curves will be constructed to determine the cumulative complication rate of the umbilical hernia in the two study arms (elective repair versus conservative treatment). Comparison will be done using the LOGRANK test. Quality of life will be compared using Repeated measurements ANOVA. The Mann-Whitney U test will be used for the analysis of the maximal observed grade per patient according to the LHCR grading tool.

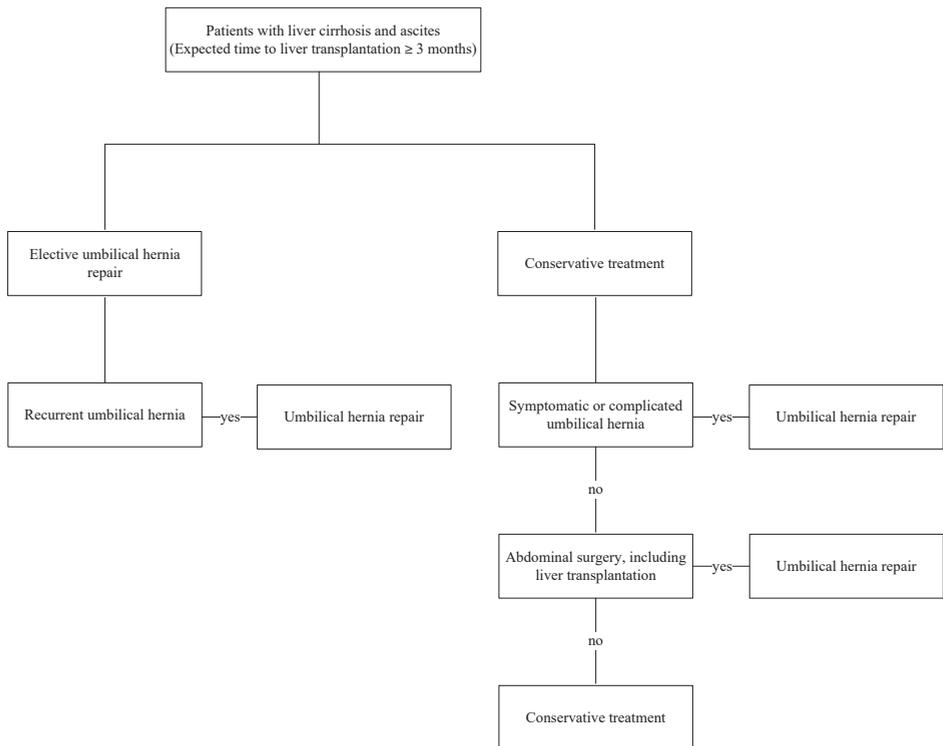


Figure 1. Flowchart.

All analyses will be conducted using SPSS (version 17.0, SPSS Inc, Chicago, USA). P-values  $<0.05$  (two-sided) will be considered statistically significant.

### **Clinical follow-up and data collection**

Morbidity will be assessed after 2-3 weeks (routine follow-up). In addition at 3, 12 and 24 months post-operative follow-up will be performed. The investigator will examine and discuss with the patients if there are any complaints related to the umbilical hernia. The patient will undergo ultrasound imaging at the 12-month follow-up to detect recurrent hernias. The patients are asked to complete a SF-36 and EQ-5D questionnaire (as part of the quality of life evaluation) at baseline, 3, 6, 12 and 24-months of follow-up. VAS will be employed to evaluate pain at baseline and after 3, 6, 12 and 24 months. In addition VAS will be done directly postoperative and at day 1 until 6 in operated cases for an umbilical hernia.

The operative data will be collected during surgery and filled out immediately after the operation by the investigator through an online case record form. The follow-up data will also be collected by the investigator, using the same system. The case record forms are only accessible by logging in to a specially designed and secured website (<https://www.crucialtrial.nl>). All personal data is coded. A data check will be performed by comparing the patient records with the completed case record forms manually. Only the coordinating investigator and the principal investigator have access to the coding system. All data are imported into a secured database on a server of our institution and are managed by the coordinating investigator, according to the hospital guidelines. All data will analyzed in collaboration with the trial statistician at the end of the trial.

### **Monitoring**

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence that results in death; is life threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome. All SAEs will be reported to the accredited Medical Ethical Committee (MEC) that approved the protocol, according to the requirements of that MEC. Serious Adverse events are major complications, unforeseen ICU admissions related to umbilical hernia or umbilical

hernia repair and reoperations. Adverse Events are minor complications, prolonged admission, readmission related to elective repair or conservative treatment.

An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters every 6 months. All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific adverse event. A copy of this report will be sent to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board. The Data Safety Monitoring Board will consist of an epidemiologist/statistician, a hepatologist and an independent surgeon.

## DISCUSSION

Management of umbilical hernia in patients with liver cirrhosis is a subject of debate.<sup>8,14,15</sup> Historically, elective hernia repair was deemed hazardous for patients with an umbilical hernia, because of the presumed increased surgical risks and the high recurrence rates after repair. Instead, watchful waiting was often advised, particularly in patients with asymptomatic umbilical hernia.<sup>3,4</sup>

More recent publications have shown that patients who are treated conservatively are at risk of developing complications of the hernia due to incarceration, rupture of the overlying skin or recurrent infections of ascites.<sup>6-8</sup> To date, no randomized controlled trial on this matter has been conducted. The CRUCIAL trial will provide level 1b evidence to support the preference for either conservative treatment or elective repair of umbilical hernia in patients with liver cirrhosis and ascites.

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