BMJ Open

Study protocol for a multicentre nationwide prospective cohort study to investigate the natural course and clinical outcome in benign liver tumours and cysts in the Netherlands: the BELIVER study

Alicia Furumaya,1,2 Martijn P D Haring,3 Belle V van Rosmalen,1,2 Anne J Klompenhouwer,4 Marc G Besselink,1,2 Robert A de Man,5 Jan N M IJzermans,4 Maarten G J Thomeer,6 Matthijs Kramer,7 Mariëlle M E Coolen,8 Maarten E Tushuizen,9 Alexander F Schaapherder,10 Robbert J de Haas,11 Evelien W Duiker,12 Geert Kazemier,13,14 Otto M van Delden,2,15 Joanne Verheij,2,16 R Bart Takkenberg,2,17 Frans J C Cuperus,18 Vincent E De Meijer,3 Joris I Erdmann,1,2 Dutch Benign Liver Tumor Group (DBLTG)

ABSTRACT

Introduction Benign liver tumours and cysts (BLTCs) comprise a heterogeneous group of cystic and solid lesions, including hepatic haemangiomia, focal nodular hyperplasia and hepatocellular adenoma. Some BLTCs, for example, (large) hepatocellular adenoma, are at risk of complications. Incidence of malignant degeneration or haemorrhage is low in most other BLTCs. Nevertheless, the diagnosis BLTC may carry a substantial burden and patients may be symptomatic, necessitating treatment. The indications for interventions remain matter of debate. The primary study aim is to investigate patient-reported outcomes (PROs) of patients with BLTCs, with special regards to the influence of invasive treatment as compared with the natural course of the disease.

Methods and analysis A nationwide observational cohort study of patients with BLTC will be performed between October 2021 and October 2026, the minimal follow-up will be 2 years. During surveillance, a questionnaire regarding symptoms and their impact will be sent to participants on a biannual basis and more often in case of invasive intervention. The questionnaire was previously developed based on PROs considered relevant to patients with BLTCs, with special regards to the influence of invasive treatment as compared with the natural course of the disease. The primary study aim is to investigate patient-reported outcomes (PROs) of patients with BLTCs, with special regards to the influence of invasive treatment as compared with the natural course of the disease.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The BELIVER study will lead to an expansion of the current knowledge on patient-reported outcomes in patients with benign liver tumours and cysts (BLTCs) in the Netherlands and the influence of interventions hereupon.
⇒ The long-term, biannual follow-up and increased frequency of questionnaires postoperatively will provide data to enable professionals to better inform patients what to expect and to enable patients and professionals to make well-informed treatment decisions together.
⇒ As the study is conducted nationwide, the extent of medical practice variation regarding management of BLTCs can be assessed.
⇒ Questionnaires are continued even after cessation of medical follow-up, which may introduce disease burden but may just as well be a confirmation of well-being for patients.
⇒ Patient burden is minimised through use of questionnaires using computerised adaptive testing.

INTRODUCTION

Benign liver tumours and cysts (BLTCs) comprise a heterogeneous group of cystic
and solid lesions. Although extensive research has been performed in the field of BLTCs, their natural course including their influence on patient reported outcomes (PROs) has been underexposed. The most common and relevant cystic lesions are simple non-parasitic liver cysts (estimated incidence of 18%) and ‘cystadenomas’ (1%-5% of all liver cysts), now referred to as mucinous cystic lesions of the liver and biliary system and intraductal papillary neoplasms of the liver and bile ducts (MCNs and IPNBs). Solid lesions include hepatic haemangioma (0.4%-20%), focal nodular hyperplasia (FNH, 0.4%-3%) and hepatocellular adenoma (HCA, 0.001%-0.004%).

Many BLTCs are found incidentally on routine imaging for unrelated pathology. The rising incidence of those so-called incidentalomas is at least partly attributable to the increasing use of non-invasive imaging modalities. Main complications of BLTCs are bleeding and malignant transformation—both of which rarely occur. Of the five most common and relevant solid and cystic lesions, only (large) HCAs and ‘cystadenomas’ have a known risk of malignant transformation. Treatment indications remain an important matter of debate. In general, treatment of BLTCs is only recommended when they either have a risk of complications or cause severe complaints often with associated impairment of quality of life. When little or no risk of complications is present, the latter is often the sole indication for treatment.

However, this recommendation has various nuances, which hampers shared decision and makes the management of BLTCs exceptionally prone to undesirable practice variation. First, the influence of treatment on PROs is important but rarely reported. Second, in the current literature, PROs after treatment by surgery or interventional radiology are rarely compared with conservative management. Finally, variations in diagnostic methods may be present, for example, FNH is easily misdiagnosed as HCA when inadequate diagnostics are applied.

Therefore, this observational cohort study aims to investigate the PROs of patients with BLTCs during their natural courses as well as after treatment. This data will enable patients and professionals to make well-informed treatment decisions together to optimise value-based outcomes. In addition, the study will provide an overview of the clinical practice in the Netherlands.

**METHODS AND ANALYSIS**

**Study design**

The BELIVER study (Natural Course and Clinical Outcome in BEnign LIVER tumours and Cysts) is an investigator-initiated, nationwide, multicentre observational cohort study. All Dutch medical centres treating patients with BLTCs are eligible for participation, facilitated and coordinated through the Dutch Benign Liver Tumor Group (DBLITG) network. The study was registered in the Netherlands Trial Register. Reporting of the study protocol and, eventually, of the full study is done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

**Study population**

Adult patients (≥18 years old) presenting with a common and/or clinically relevant BLTC at participating centres are eligible for inclusion. Clinically relevant BLTCs are defined as all BLTCs potentially eligible for either surgical intervention or follow-up. Strict cut-off values regarding BLTC size will not be defined and are assessed on a per patient basis by treating professionals.

The study will be conducted from October 2021 till October 2026, the minimal follow-up will be 2 years. Patients diagnosed with an uncommon BLTC, unwilling or unable to provide written informed consent or to fill in the questionnaire and patients with another disease substantially affecting PROs, will be excluded. Uncommon BLTCs and clinically less relevant are excluded. These include choledochal cysts, hepatic angiomylipoma and biliary hamartoma/Von Meyenburg complexes. Additionally, patients with polycystic liver disease are excluded as they form a circumscribed group of patients with very typical symptoms and treatments, including liver transplantation and they are currently already included in another international study.

**Study objectives and outcomes**

The primary study objective is to systematically record the PROs during the natural course and after (minimally) invasive treatment of patients with BLTCs. Secondary study objectives are to evaluate changes in tumour/cyst diameter and the occurrence of any mortality and complications, related to either the natural course of the disease (malignant transformation or haemorrhage) or related to tumour or cyst treatment. The study will also provide an overview of potential variation in management and outcomes of Dutch patients with BLTCs.

The primary study outcome measure is change in PROs including severity of symptoms from the start compared with the end of the follow-up period. Symptoms are measured by a questionnaire, focusing on PROs relevant to patients with BLTCs and their caregivers and partly administered through the Patient-Reported Outcomes Measurement Information System (PROMIS).

The questionnaire is administered biannually. Although a multiplicity would have enabled a more accurate longitudinal study with correction for confounding events, increasing questionnaire frequency will also probably lead to a reduction of study adherence and result in an increased patient burden. Moreover, one might argue that continuing surveys even after cessation of medical follow-up may introduce disease burden that remind patients of their diagnosis. However, the biannual questionnaires may just as well be a confirmation of well-being for patients. In addition, currently some patients might be subjected to extended periods of follow-up even in...
the absence of this study as a consequence of practice variation.

Secondary outcomes related to interventions include postoperative complications according to Clavien-Dindo Classification, the Comprehensive Complication Index, 30 and 90-day mortality and the Society of Interventional Radiology classification for adverse events. Treatment effects will be evaluated with additional questions regarding intervention indication, the effectiveness of the treatment on symptoms and the likeliness of patients to choose the treatment again. If surgical intervention is applied, questions on incisional herniation are added to the questionnaire after intervention. Supplementary questionnaires will be sent after interventions at 3, 6 and 12 months, thereafter resuming to biannual questionnaires. An example of two cases and their follow-up with questionnaires is shown in figure 1.

In addition to data collected from questionnaires, data will be extracted from local electronic patient files. This includes the following data: (1) baseline patient characteristics (age, gender, comorbidity), (2) tumour or cyst characteristics (among which diameter, imaging and histopathological examination), (3) certain data specific for the type of BLTC the patient was diagnosed with and (4) details on the intervention performed. Table 1 summarises collected variables. All tumour and cyst diameters will be measured according to RECIST V.1.1 criteria.21

**Patient involvement and questionnaire selection**

Various questionnaires have been used to evaluate PROs of patients with BLTCs. However, these questionnaires were not developed for the evaluation of outcomes of patients with BLTC and, therefore, most likely do not appropriately measure outcomes relevant to patients with BLTCs. Based on the literature and focus groups with patients with BLTCs and their caregivers, we selected relevant PROs. These were: insecurity/anxiety, pain, fatigue and limitations in daily life. The domains anxiety, fatigue, ability to participate and pain interference will be evaluated in the current study using computerised adaptive testing through the Dutch-Flemish PROMIS.22–24 PROMIS instruments have recently successfully been used in research on various patient groups.25 26 Additionally, numerical rating scales for pain (current and most, least, and average pain over a week) and two general health and quality of life questions will be assessed.

**Data collection**

Data will be collected using electronic case report forms using an online-based platform, which automatically generates patient identifiers consisting of the hospital code and a number. A subject identification log will be kept in each centre by the principal investigator or local coordinating investigator. This subject identification log will contain the personal details, which can be used to send questionnaires to patients. Only this dedicated person has the key for decoding patient data. At completion of the follow-up period, the database will be exported from the online platform. The database will be hosted on a secure server with the infrastructure, configuration and licenses that are consistent with current norms and laws to ensure safe and secure data storage and processing.
Sample size and statistical analysis

No sample size calculation was conducted as this is an observational cohort study. A previous single-centre prospective cohort study on the (conservative and surgical) treatment of HCAs and FNHs included 110 patients in 4.5 years. This current study has a broader scope as it spans across at least seven medical centres, includes more BLTC types and also includes patients treated by interventional radiological procedures. Therefore, the aim is to include at least 450 patients.

Statistical analyses will be performed using SPSS statistics for Windows V.24.0 (SPSS, Chicago, Illinois) and R for Windows V.3.6.3 (R Core Team, Vienna, Austria). Categorical data will be presented as proportions. Continuous data will be presented as mean and SD or median and IQR. Categorical variables will be compared using the Fisher exact test or the $\chi^2$ test. Continuous variables will be compared using the Mann-Whitney U test or the Student’s t test. Cox proportional hazards model will be used when appropriate. A two-tailed $p<0.05$ will be considered statistically significant.

Scores for each PRO measure at the start and end of follow-up will be compared using a paired t test, and factors associated with significant gain in these measures

<table>
<thead>
<tr>
<th>Baseline information</th>
<th>Tumour or cyst specific questions</th>
<th>Treatment characteristics</th>
<th>Intervention</th>
<th>Surgery</th>
<th>Interventional radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td>Tumour characteristics*</td>
<td>Solid lesions</td>
<td>Cystic lesions</td>
<td>Date of intervention</td>
<td>Type of approach (open, laparoscopic, robot)</td>
</tr>
<tr>
<td>Age</td>
<td>Total number of lesions at baseline</td>
<td>Focal nodular hyperplasia</td>
<td>Simple hepatic cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Location of lesion (left hemiliver, right hemiliver, bilobar)</td>
<td>Haemangioma</td>
<td>Mucinous cystic neoplasms</td>
<td>Duration of hospital stay</td>
<td>Occurrence and reason for conversion</td>
</tr>
<tr>
<td>Mortality</td>
<td>Type of lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity (ASA score and Elixhauser comorbidity index)</td>
<td>Diameter, date and modality of diagnosis</td>
<td>30-day and 90-day mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diameter, date and modality of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occurrence of misdiagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If so, revised diagnosis and diagnostic modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histopathological diagnosis with immunohistochemistry if available</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *According to RECIST V.1.1 criteria, lesions will only be measured on CT or MRI (longest diameter), measured on the transversal plane on post-contrast series. Maximum of two lesions. If the target lesion is not visible on follow-up imaging (index imaging is imaging shortest before inclusion), then the diameter of the next largest tumour will be measured. ASA, American Society of Anesthesiologists; CCI, comprehensive complication index; CD, Clavien-Dindo; MWA, microwave ablation; RFA, radiofrequency ablation; SIR, society of interventional radiologists classification for adverse events; TAE, transarterial embolisation.

Table 1: Overview of recorded variables
will be evaluated. Patients will be stratified according to treatment strategy (conservative, surgical, transarterial (chemo-)embolisation and lipiodolisation, aspiration and sclerotherapy or radiofrequency or microwave ablation). Sensitivity analyses will be performed for the type of BLTC, and for the time between questionnaires and hospital visits, as hospital visits and imaging may increase the extent of the emotional burden experienced by patients. For surgically treated patients, predictors of a complicated course (Clavien Dindo ≥3b) will also be evaluated.

**Study sites**

Initiating centres are Amsterdam UMC and University Medical Center Groningen. At least all other centres participating in the DBLTG will be included. Participating centres will at least include:

1. Amsterdam University Medical Centers, Amsterdam, The Netherlands.
2. University Medical Center Groningen, Groningen, The Netherlands.
3. Erasmus Medical Center, Rotterdam, The Netherlands.
4. Maastricht University Medical Center+, Maastricht, The Netherlands.
5. Radboud University Medical Center, Nijmegen, The Netherlands.

In order to identify and/or avoid selection bias, non-DBLTG and non-academic centres will also be enabled to join during the course of the study.

**ETHICS AND DISSEMINATION**

**Ethical considerations**

This trial will be conducted in accordance with the principles of the Declaration of Helsinki and as stated in the laws governing human research and Good Clinical Practice. The study does not interfere or change the process of treatment of the BLTCs in the included patients. The study does not interfere or change the process of treatment of the BLTCs in the included patients. The study does not interfere or change the process of treatment of the BLTCs in the included patients. The study does not interfere or change the process of treatment of the BLTCs in the included patients.

**Additional burden and risk associated with study participation**

The proposed study does not interfere with standard patient care. No additional blood samples, increase in number of hospital visits, physical examination or other tests are indicated. However, in case of cessation of medical follow-up, patients included in the study will still receive questionnaires.

There are no direct benefits for patients participating in this study. There are no risks involved with participating in this study. The additional burden of the study is considered to be minimal. Completion of the questionnaire will take approximately 15 min. The questionnaires might remind patients of their BLTC diagnosis. Some of the questions might be confronting (ie, questions regarding the impact of complaints on daily life and work).

**Administrative aspects, monitoring and publication**

All results, either positive or negative, will be published in a peer-reviewed journal. All results will be reported suiting reporting guidelines provided by the EQUATOR-network (URL: https://www.equator-network.org/). All Dutch centres collaborating in the DBLTG will be invited to participate in this study. All results originating from this study will be published on behalf of the DBLTG.

Coauthorship is available for one physician at each centre supplying at least five cases and for two physicians at each centre supplying at least 10 cases. In each centre, it may be decided individually which one or two physicians will be mentioned as coauthors. Coauthorships may also be offered to persons who contributed substantially to the conceptualisation and execution of the study. All coauthorships will have to fulfil the international committee of medical journal editors regulations.28

In addition to these coauthorships, others involved may be listed as collaborator and the journal will be asked to list them as such also in MEDLINE/PubMed. For each
centre supplying at least 30 cases, one collaborator may be included; for centres supplying at least 40 cases, two collaborators; for centres supplying 50 or more cases, three collaborators.

Author affiliations
1Department of Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
2Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
3Department of Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
4Department of Surgery, Erasmus Medical Center, Erasmus University Rotterdam, Rotterdam, The Netherlands
5Department of Gastroenterology and Hepatology, Erasmus University Rotterdam, Rotterdam, The Netherlands
6Department of Radiology, Erasmus University Rotterdam, Rotterdam, The Netherlands
7Department of Gastroenterology and Hepatology, Maastricht University Medical Centre+, Maastricht University, Maastricht, The Netherlands
8Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
9Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands
10Department of Surgery, Leiden University Medical Center, Leiden University, Leiden, The Netherlands
11Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
12Department of Pathology and Medical Biology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
13Department of Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands
14Cancer Center Amsterdam, Amsterdam, the Netherlands
15Department of Radiology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
16Department of Pathology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
17Department of Gastroenterology and Hepatology, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
18Department of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Twitter Marc G Besselink ©MarcBesselink

Collaborators Dutch Benign Liver Tumor Group (DBLTG): I D Munsterman, Department of Gastroenterology and Hepatology, Radboud UMC, Radboud University, Nijmegen, The Netherlands. D Ramaekers, Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, Vrije Universiteit, The Netherlands. M D Doukas, Department of Pathology, Erasmus MC, Erasmus University Rotterdam, Rotterdam, The Netherlands. J C Beckervordersandforth, Department of Pathology, Maastricht University Medical Center+, Maastricht University, Maastricht, The Netherlands. C van der Leij, Department of Radiology, Maastricht University Medical Center+, Maastricht University, Maastricht, The Netherlands. R Micela, Department of Radiology, Maastricht University Medical Center+, Maastricht University, Maastricht, The Netherlands. S van Koeverden, Department of Radiology, Radboud UMC, Radboud University, Nijmegen, The Netherlands. AE Braat, Department of Surgery, Leiden UMC, Leiden University, The Netherlands. MJ Coenraad, Department of Gastroenterology and Hepatology, Leiden UMC, Leiden University, Leiden, The Netherlands. SSLP Crobach, Department of Pathology, Coenraad, Department of Gastroenterology and Hepatology, Leiden UMC, Leiden, The Netherlands. MJ Braat, Department of Surgery, Leiden UMC, Leiden University, Leiden, The Netherlands. C van der Leij, Department of Radiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands. W van der Laan, Department of Pathology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands. T M van Gulik, Department of Surgery, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, The Netherlands. R Swijnenburg, Department of Surgery, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, The Netherlands.

Contributors AF, MPDH, BVVR, MGB, VEDM, JIE: conceptualisation of the study. MGB, RADM, JNMJU, MGJT, MK, MC, MET, AEB, RJdH, EWD, GK, OMvD, JVB, RBT, FJCC: investigation and data curation. AF, MPDH, VEDM, JIE: drafting of the manuscript, study coordinators. BVVR, AJK, MGB, RADM, JNMJU, MGJT, MK, MC, MET, AEB, RJdH, EWD, GK, OMvD, JVB, RBT, FJCC: methodology of the study, revision of the manuscript. AF, MPDH, BVVR, AJK, MGB, RADM, JNMJU, MGJT, MK, MC, MET, AEB, RJdH, EWD, GK, OMvD, JVB, RBT, FJCC, VEDM, JIE: approval of the final manuscript. AF and MPDH share first authorship to this paper. VEDM and JIE share senior authorship to this paper.

Funding This work was supported by a grant from the Dutch Society of Gastroenterology (Nederlandse Vereniging voor Gastroenterologie) to the Dutch Benign Liver Tumor Group, and by a personal grant from Amsterdam UMC location AMC to A Furumaya.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Alicia Furumaya http://orcid.org/0000-0001-5897-0438

REFERENCES