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Protocol Article

Open versus laparoscopic ablation of liver malignancies – a protocol for a randomised clinical trial

Lucas Alexander Knøfler[1, 2, 3], Jeanett Klubien[1, 2, 3], Peter Nørgaard Larsen[1], Kristian Schaumburg Kiim[1], Daisuke Fukumori[1], Christoph Tschuor[1], Susanne Dam Nielsen[1, 2, 3, 4, 5] & Hans-Christian Pommergaard[1, 2, 3, 4]

1) Department of Digestive Diseases, Transplantation and General Surgery, Copenhagen University Hospital – Rigshospitalet, 2) Hepatic Malignancy Surgical Research Unit (HEPSURU), Department of Digestive Diseases, Transplantation and General Surgery, Copenhagen University Hospital – Rigshospitalet, 3) Viro-immunology Research Unit, Department of Infectious Diseases, Copenhagen University Hospital – Rigshospitalet, 4) Institute for Clinical Medicine, University of Copenhagen, Panum Institute, 5) Department of Infectious Diseases, Copenhagen University Hospital – Rigshospitalet, Denmark

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ABSTRACT

INTRODUCTION. Heat-based ablation has emerged as a less invasive alternative to surgical resection for primary and metastatic liver cancer. However, when a percutaneous approach is not feasible, ablation during open surgery is often performed. Open surgery may be accompanied by an increased risk of complications, especially in patients with comorbidities or liver cirrhosis. Laparoscopic ablation may reduce morbidity while offering a similar efficacy; however, even so, no randomised studies have been conducted.

METHODS. Eighty adult patients at a high-volume hepatobiliary centre will be randomised 1:1 to either open or laparoscopic ablation. Eligible participants have at least one liver tumour amenable to ablation but unsuitable for a percutaneous approach. The primary endpoint is the rate of complications (Clavien-Dindo ≥ 2) within 30 days after surgery. Secondary outcomes include ablation success, length of stay, post-operative pain, quality of life and recovery and 90-day mortality.

CONCLUSIONS. This trial will provide the first randomised comparison of laparoscopic and open ablation for liver tumours that are not amenable to percutaneous ablation. We hypothesise that laparoscopic ablation can reduce post-operative complication rates while maintaining comparable efficacy, potentially establishing a new standard of care for selected patients.

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Liver malignancies include primary liver cancers, most commonly hepatocellular carcinoma (HCC), and metastatic disease from various primary cancers, including colorectal cancer [1, 2]. Many patients are not candidates for surgical resection or transplantation due to extensive disease burden, impaired liver function, advanced age or comorbidities. For these patients, ablation has proven valuable [1]. In fact, ablation is the recommended treatment for early-stage HCC [3]. Ablation is less invasive and usually associated with shorter hospital stays than resection [4].

Percutaneous ablation is the least invasive approach and is the gold standard for the treatment of early-stage HCC [1]. However, certain tumour locations preclude safe percutaneous access due to the risk of injury to adjacent structures or insufficient tumour visualisation. In these scenarios, open ablation is typically performed to ensure accurate needle placement. Even so, open procedures may carry an increased risk of complications, especially for frail patients with impaired liver function [5]. More than 80% of patients diagnosed with HCC have preexisting cirrhosis, and these patients carry a higher risk of complications and have a higher postprocedural mortality due to the impaired liver function and portal hypertension [1]. Therefore, a minimally invasive approach is considered especially relevant in these high-risk patients [5]. Laparoscopic ablation may offer benefits by maintaining the same tumour access as the open approach while lowering the complication rates associated with invasive surgery [6, 7].

Ablation success is conventionally defined by complete tumour necrosis, assessed by contrast-enhanced imaging one month after the procedure [8]. Early data suggest success rates of 94-100%

with both open and laparoscopic approaches, but no randomised trials have directly compared these techniques [9-12]. Observational data from our centre found a 45% complication rate after open ablation, which is comparable to the rates after liver resection [7, 13]. Conversely, reported complication rates following percutaneous ablation range from 5% to 10%, and the literature suggests that laparoscopic approaches have similarly low complication rates [14, 15]. Robust evidence comparing open and laparoscopic approaches in patients not amenable to a percutaneous approach is imperative to guide an evidence-based approach.

Trial registration: ClinicalTrials ID: NCT06304766.

Methods

Objectives

We will conduct a randomised study comparing laparoscopic to open ablation for liver malignancies. The objectives are to:

- Compare complication rates and associated parameters between the two approaches.

- Compare treatment success one month after the ablation procedure.

- Compare differences in patient-reported quality of life and recovery.

Study design and setting

This study is an investigator-initiated randomised, controlled trial enrolling patients at a high-volume hepatobiliary centre in Denmark. The aim is to compare laparoscopic with open ablation for patients who have at least one liver tumour suitable for ablation but not amenable to a percutaneous approach. The trial follows a parallel-group design with a 1:1 allocation ratio and aims to recruit 80 participants. The protocol adheres to the principles of good clinical practice and the Declaration of Helsinki, and has been approved by the Scientific Ethics Committees and the Danish Data Protection Authority.

Participant eligibility

Patients are screened during routine multidisciplinary conferences. Eligibility for the study is determined by our high-volume, multidisciplinary team. Eligible individuals must be at least 18 years old, with either a confirmed primary liver malignancy or metastatic disease to the liver for which ablation is determined to be the optimal treatment option by specialists at a multidisciplinary team conference. A tumour amenable to a percutaneous approach precludes patients from study participation. A tumour is deemed unsuitable for a percutaneous approach if:

1. The tumour is not clearly visualised with percutaneous ultrasound.

2. The tumour is located in a high-risk position where an ablation may cause damage to adjacent organs (e.g., colon, duodenum, diaphragm).

All participants must be able to understand trial procedures, comprehend and speak Danish, and provide written informed consent before randomisation.

Patients are excluded if they undergo hepatic resection in addition to ablation, cannot cooperate with post-operative protocols, or lack proficiency in Danish, thereby preventing adherence to patient-reported outcomes and proper trial follow-up. Reasons for exclusion are documented to ensure that the study population reflects the targeted clinical scenario. A comprehensive screening log will be kept for patients assessed for eligibility at the multidisciplinary team conferences.

Randomisation and allocation

After confirming eligibility and obtaining written informed consent, participants will be randomly allocated to receive either laparoscopic ablation (intervention group) or open ablation (control group). A computer-generated algorithm using a 1:1 block randomisation method will allocate a treatment approach. The block sizes are concealed from the investigators to reduce predictability in treatment allocation. In situations where the surgeon deems that the assigned approach is infeasible intraoperatively, conversion to an alternative technique may occur. The decision to convert is left to the surgeon's clinical judgement and will be documented for intention-to-treat analysis.

Procedures

All participants undergo ablation under general anaesthesia, with standard supine positioning. The ablation modality is standardised in both treatment arms, exclusively using heat-based microwave ablation with the EmprintTM system. The duration and power settings are tailored to each tumour's size and location using the manufacturer's planning software to ensure a complete ablative margin, as per standard clinical practice. Intraoperative ultrasound guides the surgeon in accurately locating and directing the ablation antenna into the target lesion.

In the open ablation arm, access to the liver is gained through laparotomy with the smallest incision possible. In the laparoscopic ablation arm, trocar placement is determined by the tumour's location in the liver and the patient's anatomy. Patients with tumours located in the posterior part of the right liver (segments 6 and 7) and cranially in segments 4 and 8 are positioned with an elevated right hemithorax (45 degrees) to allow medialisation of the liver and better tumour access. If technical challenges, such as limited working space or poor lesion visualisation cannot be resolved laparoscopically, the procedure may be converted to an open approach. A specialist group of hepatobiliary surgeons will perform all procedures at our high-volume centre all of whom are experienced and proficient in both open and laparoscopic ablation techniques. We aspire to ensure that the same surgeons perform both laparoscopic and open cases.

Post-operative analgesic management is standardised according to the assigned treatment arm and will follow the standard of care for each approach. Participants in the open ablation group will receive continuous epidural analgesia as per institutional protocol. Participants in the

laparoscopic group will be managed with a non-epidural analgesic regimen. Any complications directly attributable to the analgesic pathway will be recorded and included as a treatment-related post-operative complication.

Outcome measures

Primary outcomes

- Treatment-related complications (Clavien-Dindo Grade ≥ 2) within 30 days after ablation.

- Success rate (complete ablation response): No residual tumour on contrast-enhanced computed tomography (CT) one month after the procedure.

Secondary outcomes

- Comprehensive Complication Index (CCI): A measure integrating all complications to yield a score.

- Post-operative pain.

- 90-day mortality.

- Patient-reported outcomes: Quality of life measured with The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, cancer-specific modules (HCC18, BIL21, LM21), and post-operative recovery (QoR-15).

- Length of hospital stay.

- Procedure-related outcomes: Blood loss and need for transfusion, conversion rate (laparoscopic to open), procedure duration.

- Child-Pugh Score.

Sample size

Two primary considerations guided our sample size calculation. First, a retrospective study by our research group showed that 45% of patients undergoing open ablation experienced Clavien-Dindo ≥ 2 complications [7]. Second, in a pilot study of laparoscopic ablation conducted before this trial, we observed a 9.4% rate of Clavien-Dindo ≥ 2 complications [6].

Using a superiority design, with an alpha of 0.05 and a 90% power, a two-tailed test indicated that 62 patients in total would be required to detect a difference in complications between the two approaches. To account for an anticipated 20% loss to follow-up, intraoperative plan changes and exclusions, we will enrol 80 patients overall (40 per arm).

Additionally, we determined the sample size necessary to demonstrate non-inferiority in ablation success, anticipating a 96% success rate in both arms based on prior studies [6, 7, 9, 10]. By accepting an 11% non-inferiority margin, with an alpha of 0.05 and 80% power, we again arrived at a total requirement of 80 patients (40 per arm).

An external interim analysis will be conducted after recruiting 40 participants. The external assessors will evaluate safety. Strong evidence suggesting safety issues may subject the study to early stopping. The expected accrual rate is based on enrolment data from the run-in pilot study conducted in the study centre [16]. This establishes an accrual rate of approximately 2.7 patients per month.

Data collection

Demographic and clinical data, such as tumour characteristics, comorbidities and laboratory analysis, will be obtained from electronic medical records. Procedure-related details, including anaesthesia time, procedure duration, blood loss and any intraoperative complications, are prospectively recorded. One month after the procedure, participants undergo a contrast-enhanced CT to determine ablation success. Investigators document all complications occurring within 30 days, their severity (Clavien-Dindo grade) and any readmissions or additional interventions in the post-operative course. Ninety-day mortality will be captured through electronic medical records. Patient-reported outcomes are collected using questionnaires at baseline (preoperatively) and on post-operative days 1, 7, 14 and 30 to assess the recovery trajectory. Outcome assessment will be blinded to randomisation.

Data sharing statement

Individual participant data (including data dictionaries) and anonymised participant data necessary to replicate the statistical methods presented in the final manuscripts will be shared. The statistical analysis plan, randomisation algorithm and any analytic code will be available following publication of manuscripts containing the primary study endpoint. Data will be available to researchers who submit a study proposal and to any methodologically sound research purpose. Proposals may be submitted to the corresponding author of this protocol article.

Statistical analysis

Statistical significance will be defined as a two-sided p-value < 0.05.

Data analysis will follow an intention-to-treat approach, supplemented by per-protocol analyses. The complication rate (Clavien-Dindo ≥ 2) will be compared between laparoscopic and open ablation arms using the Chi-squared test or Fisher's exact test. The effect sizes will be expressed as risk differences and relative risks with 95% confidence intervals. Outcomes involving categorical data, such as ablation success and conversion rates, will similarly be assessed using the Chi-squared test or Fisher's test. Outcomes involving continuous data measured at a single time point (e.g., Comprehensive Complication Index) will be compared using the Mann-Whitney U test. For our longitudinal patient-reported outcomes collected at multiple time points, we will use a linear mixed-effects model to test for differences in recovery trajectories between treatment arms. The Kaplan-Meier estimator will be used to describe differences in 90-day mortality between treatment arms, with log-rank tests for significance. For the secondary outcomes, p-values will be adjusted for multiple comparisons using the Holm-Bonferroni method.

Discussion

This randomised controlled trial addresses a central clinical dilemma in patients with liver cancer by providing a direct comparison between laparoscopic and open ablation techniques for tumours that are unsuitable for percutaneous ablation. To our knowledge, the OPTIMAL trial is the first to investigate whether laparoscopic ablation, as a minimally invasive alternative, can reduce post-operative morbidity without compromising the therapeutic efficacy seen with the traditional open approach.

The primary hypothesis tested by this study is that laparoscopic ablation will significantly reduce post-operative complications occurring within 30 days compared with open ablation without compromising treatment efficacy. Our pilot data indicated that laparoscopic ablation is a feasible option with a high ablation completeness and a low risk of complications [6].

However, some limitations to laparoscopic ablation must be acknowledged. Tumour visualisation and accurate antenna placement are critical to the success of ablation. Technical challenges during the procedure may result in conversion to an open approach to avoid a futile procedure that may subsequently require additional procedures, thereby negating the benefits of the minimally invasive approach. In recent years, advanced stereotactic navigation tools have expanded the reach of ablation [16]. However, these methods are not currently implemented at our study centre. Therefore, the findings of this study will primarily apply to centres with a similar technological setup.

Should laparoscopic ablation demonstrate superior outcomes or even equivalence in efficacy with reduced morbidity, this may lead to a shift in the surgical management of liver malignancies, promoting minimally invasive approaches as the standard of care. Conversely, findings favouring the open approach would solidify its continued role as the standard of care for patients who are not amenable to percutaneous ablation.

conclusions

This trial could be a critical step towards establishing evidence-based guidelines for the optimal surgical management of liver malignancies that are unsuitable for percutaneous ablation.

Correspondence *Hans-Christian Pommergaard*. E-mail: hans-christian.pommergaard@regionh.dk

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