1. Title

Laparoscopic versus open ablation of liver malignancies: a randomized, controlled multicenter trial

2. Aims

We will conduct a randomized study to compare laparoscopic ablation for liver tumors with the standard care (open ablation) with the hypothesis to reduce complications and maintain similar treatment success rate. We will

- Investigate differences in complications (primary outcome), length of hospital stay and mortality between laparoscopic and open ablation.
- Investigate differences in success rate (complete ablation response) between laparoscopic and open ablation.
- Investigate differences in quality of life between laparoscopic ablation and open ablation and explore how patients with liver tumors experience ablation of a liver tumor.

Background

Surgically treated malignancies in the liver include primary liver cancers and liver metastases. Hepatocellular carcinoma (HCC) accounts for almost 90% of primary liver cancers, which is the sixth most common cancer worldwide and the fourth leading cause of cancer-related death globally.[1, 2] Furthermore, hematogenous spread of other cancers to the liver is very common due to the dual vascular supply, arising from both systemic arterial and portal venous systems.[3] The most common primary site is colorectal cancer, however, depending on age and sex a wide range of primary cancers spread to the liver including breast, pancreatic, and neuroendocrine cancers.[4-9] Patients with liver metastases have significantly reduced survival compared to those without liver metastases.[4, 5, 10]

Many patients suffering from liver malignancies are not candidates for surgical interventions such as transplantation or hepatic resection due to extensive tumor burden, underlying liver disease, age, or other comorbidities. For some of these patients, ablation has proven to be a valuable alternative that is less invasive with fewer complication and with a shorter postprocedural hospital stay compared to resection.[11] In addition, it preserves more of the liver parenchyma than resection which is especially important in patients with impaired liver function.

Ablation therapy is often guided by real-time ultrasound and can be performed either percutaneously, by laparoscopy or by laparotomy (open). Percutaneous ablation is the least invasive approach and is gold standard for the treatment of HCC and liver metastases when possible.[12, 13] However, some tumors may not be accessible percutaneously due to risk of injury to adjacent organs or due to insufficient visualization of the tumor. Ablation during open surgery allows treatment of tumors in locations difficult to reach percutaneously. At present, patients who cannot be treated percutaneously are offered open ablation in most centers. However, open surgery may be associated with a higher risk of complications which may be devastating for frail patients and patients with impaired liver function.[14] More than 80% of patients diagnosed with HCC have preexisting cirrhosis[15, 16], and these patients are at a higher risk of complications and have a higher postprocedural mortality due to the impaired liver function and portal hypertension.[13, 17-19] Therefore, a minimally invasive approach is considered especially relevant in these high-risk patients. Laparoscopic ablation is less invasive with a presumed lower complication rate than the open approach, however, offers some of the same advantages needed for tumors in locations not favorable for percutaneous ablation.

Success of the procedure is demonstrated by a complete ablation of the macroscopic tumor assessed by contrast-enhanced ultrasound or CT one month after procedure.[20] Previous studies reported a complete ablation achieved in 94-100% of patients treated with ablation with no significant difference between percutaneous, laparoscopic, or open approach.[8, 21-27] However, no comparative study has been performed.

A study from our department found complications in 45% of open ablations based on the Clavien Dindo Classification which was comparable to that of patients undergoing liver resection.[28] An external study found comparable results of 39.5%.[29] In contrast, the complication rate after

percutaneous ablation is as low as 5%[30] and the literature suggests that laparoscopic approach have similar low complication rates.[31, 32]

Previous studies

No previous randomized studies or even comparative studies have been carried out investigating this subject. The literature consists of few smaller reports of case series [31, 32]. These reports support that laparoscopic ablation is both safe and efficient.

3. Method

The study is a randomized, controlled, multicenter study in patients with liver malignancies treated at the four Danish liver surgery centers (Rigshospitalet, Odense, Århus and Aalborg). Patients with one or more liver tumor suitable for ablation as primary treatment, but not amenable for percutaneous ablation will be randomized between laparoscopic and open ablation. Opaque envelopes with patient numbers containing the randomization sequence will be opened after informed consent has been obtained. We plan to include 80 patients with 40 patients per arm. Patients will be randomized 1:1 (see below). Randomization will be stratified on center level to ensure comparable populations between the groups within each center.

Due to perioperative findings, the treatment to which the patient is randomized to may be considered not feasible or inappropriate, e.g. due to insufficient visualisation of tumor or findings that warrant a different treatment strategy. In these cases, the treatment strategy is based on the surgeons preferences. In laparoscopic cases, a minimally invasive approach should be maintained if possible, e.g. by combining laparoscopy with percutanous ablation needle placement.

Ninety days after the procedure, the patient chart will be evaluated to register patient characteristics and outcomes. Moreover, at one month all patients will receive a CT-scan to evaluate success rate (complete ablation response). The CT-scan is part of standard of care, it is assessed by an experienced radiologist, and it is not part of this study. Before surgery and one month after, health related quality of life (HRQoL), the psychological burden and level of recovery will be assessed. Open ablation is standard of care. Thus, the intervention group will receive a treatment with assumed fewer compliations and similar success rate.

Treatment and follow-up

Patients will be randomized 1:1 between ablation during open surgery and laparoscopic ablation

Ablation procedure

The procedure will be performed in general anesthesia and with the patient in supine position on the operating table. The laparotomy or laparoscopy will be performed by a surgeon specialized in liver surgery. A perioperative ultrasound is performed to visualize and to guide the electrode into the tumor. Using a heat-based ablation modality which generates high temperatures, the tumor cells are destroyed leaving an ablation zone. Included center may used either radiofrequenly ablation and micwowave ablation as modality. However, the modality should be the same in both groups in each center.

Endpoints and outcome measurement

Primary outcome

- Treatment-related complications that develop within 30 days following ablation will be reported according to the Clavien-Dindo Classification, which is considered the best validated classification to rate surgical complications.[33] The primary outcome is defined as any complication (Grade 2 or above) in the Clavien-Dindo Classification.

Secondary outcomes

- Success rate of the procedure is described as rate of complete ablations one month after procedure. A complete ablation response is defined as complete absence of enhancing tissue at the tumor site after one month on CT-scan.[20]
- Complications reported as Comprehensive Complication Index (CCI). CCI is a scoring system for overall morbidity and is reflected on a scale from 0 (no complication) to 100 (death). It is based on Clavien-Dindo classification and takes all complications after a procedure into account.[34]
- Highest complication grade according to the Clavien-Dindo Classification
- Wound infections within 30 days is defined as wound dehiscence requiring secondary suturing or treated conservatively. Fascial dehiscence will be recorded separately.

- Postoperative liver failure is defined by the "50-50 criteria" (prothrombin time <50% and serum bilirubin >50 µml/L on postoperative day five).[35]
- Postoperative pain will be assessed by Visual Analogue Scale for acute and chronic pain, pre-operatively and on each post-operative day until discharge, after seven days, 14 days and one month.[36]
- Overall and disease-free survival.
- Procedure related mortality within 90 days.
- HRQoL before and one month after the procedure will be assessed using the Danish version of The European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ C30)[37] and a disease specific form for patients with HCC (QLQ HCC18),[38] cholangio carcinoma (QLQ BIL21)[39] or colorectal liver metastases (QLQ LM21).[40] Depression and anxiety will be assessed before and one month after procedure using PHQ-9 and GAD-7, respectively.[41, 42] Recovery will be assessed with the Quality of recovery (QoR-15) before and seven days after the procedure.[43]
- Length of hospital stay defined as time in days from operation to discharge.
- Blood loss during surgery
- Need for perioperative blood transfusion
- Conversion rate in the laparoscopic group
- Duration of procedure
- Model for Endstage Liver Disease (MELD) and Child-Pugh score before operation and on postoperative day five.
- Patients experiences of undergoing ablation will be explored by individual interviews one months after the procedure.

Feasibility and timeline

The project will be carried out at the four Danish liver surgery centers (Rigshospitalet, Odense, Århus and Aalborg). Office space and facilities will be provided. The project group includes experienced researchers and surgeons specialized in liver surgery.

In 2019 and 2020, approximately 45-50 patients each year with liver malignancies were treated solely with ablation during open surgery in Rigshospitalet. The majority of these patients may be included in the present study. Approximately half of the procedure in Denmark are performed at Rigshospitalet

with the remaining distributed between the others centers in Odense, Århus and Aalborg. Thus, we expect that all patients for this study can be recruited in approximately 1.5 years (see sample-size calculation). The procedures will be performed by experienced liver surgeons to maintain the technical skills required.

The project will form the basis of a PhD project and results will be published in international peer-reviewed scientific journals. The PhD-student will handle inclusion at Rigshospitalet, follow-up, data collection, statistical analyses, and writing of three papers. A PhD-student will be hired through the job portal of Copenhagen University and sundhedsjobs.dk. Based on interviews, we will hire the best qualified candidate. The study group members in Odense, Århus and Aalborg will handle inclusion of patients and perform the procedures in their own center. The study has been funded from The Danish Cancer Society "Knæk Cancer", which covers three year salary for a PhD-student and a 20% research position designated to the primary investigator.

Study group

Department of Surgery and Transplantation, Rigshospitalet:

- Hans-Christian Pommergaard (primary investigator), Lucas Knøfler (PhD-student), Peter Nørgaard Larsen, Christoph Tschuor, Daisuke Fukumori, Christian Ross Pedersen, Nicolai Schultz, Jens Hillingsø, Allan Rasmussen, Paul Krohn, Stefan Burgdorf, Jan Storkholm, Carsten Palnæs, Martin Sillesen, Susanne Dam Poulsen, Kristine Dengsø and Jeanett Klubien (PhD-student)

Department of Surgery, Århus Universtiy Hospital

- Anders Riegels Knudsen

Department of Surgery, Odense University Hospital

- Claus Wilki Fristrup

Department of Surgery, Aalborg University Hospital

- Mogens Stender

4. Statistical considerations

We will use descriptive statistics and the dataset will be described with frequencies and percentages for categorical variables and means or medians for continuous variables. Primary outcome and rates of secondary dichotomous outcomes will be compared between the groups using Fischer's exact test. Mean VAS score will be compared using Mann-Whitney U-test. To determine risk factors affecting ablation response, logistic regressions will be used in both univariable and multivariable analyses. The EORTC Quality of Life questionnaire is designed to measure cancer patients' social, physical, and psychological functions. Quality of life will be reported using the summary score with the intention of comparing patients treated with either laparoscopic or open ablation. Mann-Whitney U-test will be used to assess differences in the summary scores. Analyses will be performed both on intention-to-treat and per protocol levels. The level of statistical significance will be set to $p<0.05$. All statistical analyses will be performed using R, version 4.0.3.

Sample size

Based on a previous study from our center[28], the primary outcome (any complication Grade 2 or above, Clavien-Dindo Classification) occurred in 45% of patients undergoing open ablation. The similar complication rate from another external study was 39.5%.[29] The hypothesis is that with a laparoscopic approach, the complication rate can be reduced to 10%. With an alpha of 5% and power of 80%, we will need 60 patients (30 in each arm).

The rate of complete ablation in one month is approximately 95% for open ablations.[44-46] Using a non-inferior approach and assuming a similar rate of complete ablation in the laparoscopic group, we will need 54 patients (non-inferiority limit 15%, alpha 5% and power 80%).

By including 80 patients, both above sample-size calculations will be covered, and we will have sufficient material compensate for possible excluded patients. Before randomization, we will perform training of laparoscopic ablation using a training fantom developed for the purpose. Accuracy of laparoscopic needle placement with ultrasonography will be assessed using a gel with artificial tumors and an artificial abdominal wall. In addition, we will perform 20 cases with laparoscopic ablation to ensure that technique and learning curve is sufficient compatred with our standard of care (open ablation). At this point, sufficient safety and efficacy (comparable to the litterature) will be

ensured prior to randomization and additional cases and additional training may be performed is nescessary.

After randomization of the first 15 laparoscopic cases, we will perform an interim analysis looking only at conversion rates in the laparoscopic group due to lack of feasibility. In case of a conversion rate above 20%, sample size will be increased according to the conversion rate, e.g. 20% more patients in each group with a conversion rate of 20%. This is done to ensure suffcient power in our comparison between the open and laparoscopic technique.

5. Patients

Inclusion criteria: one or more tumors not amenable to percutaneous ablation, age > 18 years, signed informed consent, diagnosis of primary liver cancer or liver metastases from any primary tumor, and tumor suitable for ablation as primary treatment

Exclusion criteria: ablation performed in conjunction with resection, patients who cannot cooperate with the study, and patients who do not understand or speak Danish

6. Risks, side effects or disadvantage for the patients

All procedures will be done in general anestesia with specialized post-operative pain management. Patients are randomized between the standard care (open ablation) and laparoscopic ablation. Laparoscopic ablation is less invasive including small incision with assumed less pain and risk of postoperative ablation. All side effects should be less severe compared with standard of care. The main possible disadvantage for the patients would be if laparoscopic ablation had less treatment success rate compared with open due to limitation in tumor visualization with ultra-sound or placement of ablation needle in the tumour. In laparoscopic ablation, the needle is placed transabdominally compared with open ablation, where the needle is placed directly in the liver. If the success rate was lower, this would entail a risk of subsequent open procedure to ensure sufficeint ablation of the tumor. However, previous reports suggest a similar success rate for laparoscopic ablation compared with open [31, 32]. Thus, we consider this risk to me minimal.

7. Biological material from research subjects

We will not collect biological material from the patients for the study.

8. Information from patient records

Patient information will be retrieved from patient electronic charts. Patient characteristics include cancer diagnosis and stage, age, gender, primary liver disease, co-morbidities, MELD-score (patients with HCC), Child Pugh-score (patients with HCC), previous surgery, viral infections and medical comorbidities. Thirty days after the procedure, information regarding success rate of ablation, complications and lengths of stay will be collected from the electronic records. Ninety days after the procedure, procedure related mortality will be recorded. At the end of the study, complete follow-up regarding overall and disease-free survival will be recorded. The collected information will be used to assess primary and secondary outcomes and to assess whether patient characteristics are equally distributed between the two treatment groups.

The primary investigator and sub-investigators have direct access to obtain information in the patient's medical record which is necessary to carry out the research project and for control purposes, including self-control, quality control and monitoring, which they are obliged to carry out.

The information to be used in the project before consent is given from the subjects is passed on to the primary investigator.

9. Processing of personal data in the project

The General Data Protection Regulation (GDPR), the Danish Data Protection Act, and the Helsinki II declaration are observed and will be complied with unconditionally.

Throughout the project all patient information will be labeled with non-personal identifiers (pseudo-anonymized). Information to identify individual patients will only be available to the study

coordinator Hans-Christian Pommergaard and will only be used if it becomes necessary to collect new clinical information from the patient files.

Collected data will be registered in a Case Report Form (CRF), this and the patient record will be made available to third parties in accordance with Danish legislation, e.g. in connection with inspection by authorized representatives from relevant authorities. Patients will be informed about the possibility of an audit by public authorities.

No data or patient information are transferred outside this country.

10. Economy

This is a researcher-initiated study. The initiative to establish the study was taken by the primary investigator, Hans-Christian Pommergaard. The study has been funded from The Danish Cancer Society “Knæk Cancer 2022” with 2,231,250 DKK. The funding covers salary for a PhD-student in three years and a 20% research position in three years for Hans-Christian Pommergaard. Funding for additional ultra-sound equipment for laparoscopic ablation has been sought from The Independent Research Fund Denmark (DFF). However, this equipment is not mandatory to initiate the project. These are no additional expenses for the involved departments associated with the project. The partners in this project have no financial interests in the project.

11. Remuneration to participants

The patients do not receive remuneration in connection with this study.

12. Recruitment of subjects and informed consent

The participants are among the patients who are already referred for treatment of a liver tumor at the included centers. These patients are identified by a clinician, and informed about the possibility of being informed about the project.

After a joint decision between a specialist and the patient about ablation of a liver tumor not amenable for percutaneous ablation, typically at the first visit to the surgical outpatient clinic, and after it has been ensured that the inclusion and exclusion criteria are met, the patient will be oriented about the project and offered written and oral information.

Interested patients are informed orally and given written participant information. The patient will be offered an in-depth interview during the day. During the interview, the patient will receive verbally sufficient information about the purpose and structure of the study, as well as potential risks and disadvantages. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time, without this having an impact on their further progress in the department. They will also be informed that they may be withdrawn from the study at the discretion of the investigator responsible for the study.

The patients will also be informed about the treatment they will be offered if they choose to say no to participating, and they will also be informed that all data will be treated confidentially.

A copy of the information and signed declaration of consent will be given to the patient and a copy will be kept in the medical record. Current regulations from the Scientific Ethics Committee regarding informed consent will be followed.

It is the responsibility of the primary investigator that all patients receive oral information, so that it is ensured that the patient is completely aware of all aspects of participation in the study. The patient can withdraw his consent to participate in the study at any time. If the patient decides to do this, it will not impair his or her relationship with investigators or other staff, and the patient will continue to receive the best treatment the department can offer.

The conversation with the patient will be handled by the investigator, or a person with delegated responsibility for this, when the patient accepts ablation as treatment in the outpatient clinic, and will take place in a calm environment and with the possibility for the patient and any relatives can ask questions. By written summons, the patient is invited to have a relative with him/her on the day of the outpatient interview.

The patient can give informed consent immediately at the outpatient interview, where the decision on ablation as treatment and project information have taken place. Alternatively, the patient can be offered a new interview after a few days of reflection. Longer reflection time will not be appropriate for the patient's treatment, as this could delay the time to surgery. If the patient so wishes, he/she will be offered time to think before giving consent until the morning of the operation day.

When it is ensured that the patient has understood the information given, had the desired time to think, and has received answers to any questions, informed consent is sought.

13. Publication

Positive, negative and non-conclusive results are published in international peer-reviewed journals. Authorship will be offered based on fulfilment of the ICMJE criteria.

14. Ethical considerations

Currently, ablation during open surgery is the standard of care for tumors not amenable for percutaneous ablation. Compared with laparoscopic technique, open surgery is associated with higher risk of complications and post-operative pain. However, currently there is insufficient evidence to use laparoscopic ablation of liver tumors as the standard of care. The current study has the potential to provide this evidence.

Laparoscopic ablation is less invasive including small incisions with assumed less pain and risk of postoperative ablation. All side effects should be less severe compared with standard of care. The main possible disadvantage for the patients would be if laparoscopic ablation had less treatment success rate compared with open due to limitation in tumor visualization with ultra-sound or placement of ablation needle in the tumour. If the success rate was lower, this may entail a subsequent procedure to ensure sufficeint ablation of the tumor. However, previous reports suggest a similar success rate for laparoscopic ablation compared with open.[31, 32] Thus, we consider this risk to me minimal. Even so, we consider that lower complication would outweight the risk of a subsequent treatment. Moreover, if success rate was initially lower in the laparoscopic group, this

would likely improve with more experience with the technique among the surgeons. Thus, included patients as well as future patients will likely receive terapeutical benefit with the study.

The study will be conducted in accordance with the principles of the Helsinki Declaration. Approval will be obtained from the local Scientific Ethics Committees and the Data Protection Authority before the start of the study. The investigator responsible for the study will also inform the Scientific Ethics Committee of significant or major changes in the protocol, and the study will be conducted in accordance with current regulations for clinical studies on humans. All patients participating in the study must provide oral and written informed consent before being included in the study. The patients are informed that the consent includes obtaining relevant medical record information related to their current admission, as well as that this information will be submitted upon inspection by relevant authorities.

Patients are evaluated regarding depressive symptoms using the PHQ-9 questionaire[42]. The score from PHQ-9 correlates with risk of major depressive disorder.[47] Patient scoring 20-27 (severe), 15-19 (moderately severe), 10-15 (moderate), 5-9 (mild) and 0-4 (minimal) will have major depressive disorder in 34.1%, 34.1%, 19.5%, 9.8% and 2.4% of cases, respectively. If a patient in the study scores 15 or above or if the patient is deemed at risk for suicide, a psychiatrist will be consulted immediately. Patients scoring between 5 and 15 will be advised to seek medical counseling regarding evaluation of depression.

15. Patient compensation scheme (patient erstatningen)

The study is covered by the patient compensation scheme. For any injury caused directly or indirectly by the intervention in this clinical study, the hospital in question assumes the legal responsibility on behalf of the investigator responsible for the study and his staff. This is provided that the investigator responsible for the study and his employees have followed the instructions given in this protocol and any supplements thereto, and that these persons have carried out the study scientifically and in accordance with current rules and accepted techniques. In the event of injury or death unrelated to the completion of the study, the patient is insured by each individual hospital's insurance.

Laparoskopisk versus åben ablationsbehandling af levertumorer: et randomiseret, kontrolleret studie

Version 3, 01/05/2023

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