Stereotactic body radiation therapy vs. percutaneous microwave ablation for colorectal cancer patients with metastatic disease in the liver – a randomized phase II trial

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1. Background
Colorectal cancer is one of the tumor sites that most often presents with oligo recurrence. The number of metastases generally accepted as truly “oligo” are less than or equal to five in no more than three different organs. Resection remains the first option for treatment of liver metastases, but is often not the preferred treatment for technical or medical reasons. Patients can be considered for percutaneous microwave ablation (MW-ablation) or stereotactic body radiation therapy (SBRT) [1] and 5-year survival can be expected to be in the range 15-50% depending on case selection, but there is an acknowledged lack of evidence in the field.

MW-ablation is one of the most used non-surgical methods for ablation of liver metastases, but it has limitations related to the size and location of the target lesions.

SBRT is a non-invasive technique based on high-precision high-dose radiotherapy suitable for treatment of small targets in the body. SBRT has proven effective to gain tumor control with reported local control rates of 80% after 3 years [2].

No randomized studies exist comparing clinical results from MW-ablation and SBRT.

2. Study design
This study is a randomized phase II trial between MW-ablation and SBRT – two standard treatment modalities for colorectal patients with metastatic disease in the liver. The study will assess time to local lesion progression and is designed to have the ability to detect large differences in efficacy between the trial arms. In the absence of such large differences in efficacy, the protocol will for the first time provide descriptions of toxicity profiles in comparable populations treated with the two modalities and provide input to the design and feasibility of larger phase III trials.

2.1 Purposes
1. To investigate SBRT as an alternative to percutaneous MW-ablation in patients with colorectal liver metastases sized ≤4.0 cm found eligible for percutaneous thermo-ablation as first choice of treatment by the local HPB multidisciplinary team. Does SBRT prolong freedom from local lesion progression compared to MW-ablation without decrease in overall survival (OS)?
2. To establish prognostic factors for patients with colorectal liver metastases undergoing MW-ablation or SBRT
2.2 Hypotheses
In patients with colorectal liver metastases sized ≤4.0 cm the use of SBRT provides a different freedom from local lesion progression than MW-ablation.

2.3 Endpoints
Primary endpoint: Freedom from local lesion progression
Secondary endpoint: OS, ≥ grade 3 toxicity, toxicity profile as descriptive statistics

3. Study population
Our hospital gets referrals for more than 600 colorectal cancer patients with liver metastases each year. Patients fulfilling the eligibility criteria (see inclusion and exclusion criteria below) should be amenable for both treatment arms and the multidisciplinary team should agree that both MW-ablation and SBRT are safe treatment options. Eligible patients willing to be a part of the protocol are randomized after the signed informed consent is obtained. Patients are randomized 1:1 between the two treatment arms and will be analyzed according to the intention-to-treat principle. Patients will be offered to cross over to the alternative treatment arm if it turns out - after the pre-screening - that the assigned treatment arm is not a safe treatment option. Another treatment will be offered if none of the treatment arms are considered safe. We plan to include 100 patients in the study (see statistical considerations below).

3.1 Inclusion criteria
1. Colorectal cancer patients with oligo metastatic disease in the liver (1 to 3 tumors), and where metastases are found unsuitable for resection because of
   a. non-resectability
   b. small metastasis localized deep in the liver, where a parenchyma sparing intervention is preferred over an extensive resection
   c. previous extensive liver surgery
   d. comorbidity
2. The multidisciplinary team should all agree that both percutaneous MW-ablation and SBRT are safe as first treatment choice for the individual patient.
3. Tumor sizes ≤ 4.0 cm
4. Age ≥ 18 years
5. Signed informed consent
3.2 Exclusion criteria

1. Previous radiotherapy to the liver
2. Liver volume < 700 ml
3. Another active cancer disease within the past 36 months
4. Not able to understand written or oral protocol information

Curative treatment of extrahepatic disease has to be initiated in patients with lung metastases and/or primary tumors.

5. Treatment

Patients are randomized 1:1 between

- Treatment arm A: MW- ablation
- Treatment arm B: SBRT

4.1 MW- ablation procedure

MW- ablation for cancer is a minimally invasive procedure, using high-frequency microwave energy to heat tissue and thereby destroy cancer cells. During MW- ablation for cancer, imaging is performed by means of CT or ultrasound, to guide a thin needle through the skin or through an incision and into the cancer tissue. High-frequency energy passes through the needle and kills the nearby cells. The patient is fully anesthetized during the treatment.

4.2 SBRT procedure

Treatment planning

Imaging for the treatment planning will be performed according to departmental guidelines for treatment and management of respiratory motion: 4D CT in free breathing with intra-venous contrast, followed by one or three breath hold CT scans (deep inspiration or expiration), depending on whether the treatment will be in free breathing (one scan) or in breath hold (three scans).

Renography will be performed to monitor kidney function before treatment in patients where the kidneys can be expected to receive radiation. The renography is performed with technetium mag3 following the standard protocol at Rigshospitalet.

Target(s) and organs at risk will be contoured by an experienced radiologist and clinical oncologist.
Image guidance
The planning procedures for SBRT include implementation of three gold markers in order to identify the tumour on the planning CT and on the cone beam CT (CBCT), used for daily image guidance.

Treatment
SBRT: 3 fractions of 15 Gy (in total 45 Gy), 3 fractions per week. The dose is prescribed to the planning target volume (PTV) encompassing 67% isodose. The SBRT plan is normalized such that the mean dose to the gross tumor volume (GTV) is 100% = 67.5 Gy. The SBRT will be delivered in either free breathing or breath hold.

4.3 Follow-up
Patients will be followed for 5 years after treatment:
1. CT of thorax and abdomen and toxicity scores
2. Biochemical control of liver function and carcinoembryonic antigen (CEA)
3. Quality of life registration using EORTC QLQ-C30

6. Statistical considerations
The protocol is designed as a randomized phase II trial to provide descriptive statistics of the incidence of local lesion progression and toxicity profile with the two studied modalities in comparable cohorts of patients. Patients will be analyzed according to the intention-to-treat principle. In the complete absence of randomized trials in the literature we design the trial to be able to detect large differences in efficacy, defined as time to local lesion progression, as follows:

Sample size estimation
It is assumed that freedom from local lesion progression in one trial arm is 94% after one year in one arm and 85% after one year in the comparing arm, corresponding to a hazard ratio of 0.38 between trial arms. It is assumed that patients are accrued over three years with one year additional follow-up and a median time to event of 4 years. In this case, a sample size of 35 patients will yield a power of ~80% to observe such difference with an associated type I error of 5%. We plan accrual of 50 patients per arm in order to account for loss of patients to competing causes and to account for intention to treat analysis of patients crossing over.
In practice, we expect that the difference between the trial arms is smaller, in which case the main knowledge generated will be descriptive statistics of toxicity and local lesion control in the two treatment modalities and information about the possible benefits of a full phase III trial as a follow-up due to the comparable cohorts secured by randomization. For comparison, some of the best data available on SBRT is a single institutional retrospective series published in the leading radiotherapy journal in 2017 with 70 patients [3].

Kaplan-Meier curves of time to local lesion progression with confidence bands will be provided as a key outcome of the trial.

7. Risks, side effects and disadvantages

7.1 MW-ablation
In a period of 1-2 weeks after MW-ablation, the patient can sometimes experience influenza-like symptoms. The risks in relation to the procedure include bleeding, lesions in major gall-vessels with or without gall-leakage, perforation of the intestine and other adjacent structures. Complications are generally rare.

General anesthesia is associated with very low risk of complications. Moderate side effects are nausea and headache.

7.2 SBRT
Some patients will experience moderate toxicities short after treatment such as nausea (~35 in 100 patients), diarrhea (~25 in 100 patients), skin reactions (~15 in 100 patients) [4] and pain in the treated area. SBRT is associated with an increased risk of sever toxicities as hepatic failure (~1 in 100 patients), colonic perforation (~1 in 100 patients) and duodenal ulcer (~2 in 100 patients) [4].

If renography is performed, the patient might experience discomfort from injection of the tracer technetium Mag3.

8. Information from medical records
Information from medical records will be recorded and stored in RegionH approved databases (RedCap) in accordance with the rules of the Data Protection Authority. The information will include comorbidities
required for the calculation of a Charlson comorbidity score, baseline disease data and all follow-up information related to control of the treated lesions. The purpose of data acquisition is to provide descriptive statistics of the influence of patient and disease status on the compliance and precision of treatment and to assess the efficacy of the delivered treatment.

The project investigator will have access to withdraw necessary information from patient records to accomplish the quality assurance of the project but only information already recorded and stored in the databases will be used.

9. **Respect for the subjects’ physical and mental integrity and privacy**
Data collection will be reported to the Danish Data Protection Authority as part of the collective reporting performed by the Capital Region of Denmark, and following Rigshospitalet’s standard procedure. All information will be protected according to Danish data protection authority regulations and health law. The subjects and their relatives will be informed orally and in writing that participation is voluntary and that they may withdraw from the trial at any time, without providing reason. The Danish law on processing of person data will be obeyed.

10. **Economy**
All costs associated with the standard cancer treatment will be defrayed by the Danish national healthcare system. The project is initiated by the investigators at Rigshospitalet. We have received 169.500 USD from Varian Medical Systems (radiation oncology treatments and software vendor) for the current project and associated projects in liver SBRT. The funding will be a part of the ordinary salary of researchers at the department. Therefore, the researches do not have economic gain in carrying out the research project. The funding from Varian will be used to pay salary for PhD student physicist Line Stick, senior physicist Mirjana Josipovic and chief consultant Signe Risum, all part time allocated to the current project. All funding is managed via Rigshospitalet’s accounting system. Conflict of interest related to the company support will be declared in all disseminations of the results. The investigators will attempt to acquire further funding from foundations which, if successful, will be managed according to the same principles. The Committee on Health Research Ethics in the Capital Region of Denmark and study participants will be informed if further funding is achieved.

11. **Compensation**
The study participants will not be offered financial compensation for participating in the study.
12. Patient information
Patients with liver metastases are referred to the multidisciplinary conference at Rigshospitalet. Patients fulfilling the inclusion criteria will be informed about the project at the following consultation. The patients will be information of their right to be accompanied by a family member, friend or acquaintance. The written participant information and the additional documents “Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt” and “Før du beslutter dig” will be handed out. The project will be presented in an easily understood manner without the use of technical or biased vocabulary. The interview is based on the written participant information and will take place undisturbed in an interview room. The participants are offered time to reflect for 24 hours before the informed consent is obtained. All participation is voluntary and the consent can be withdrawn at any given time.

13. Dissemination of results
The results of this study, including negative or inconclusive results, will be published in international peer-reviewed scientific journals. Several manuscripts will be written and authorship will be decided according to the Vancouver guidelines.

14. Ethical considerations
The multidisciplinary team should agree that both MW-ablation and SBRT are safe treatment options. Both treatment arms’ therapies are therapy techniques used in the clinic following a standard procedure. The protocol complies with the Helsinki Declaration and national requirements for studies of patients with cancer. Patients will be fully informed about the treatment modalities and the risk of participating.

15. Patient compensation
The participants in the study are covered by the Patient Compensation Association.

References
