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

Principal investigator

Signe Normann Risum, MD, PhD
Department of Oncology, Rigshospitalet

Investigators

Ivan Richter Vogelius, PhD, DMSc
Department of Oncology, Rigshospitalet

Mirjana Josipovic, MSc
Department of Oncology, Rigshospitalet

Line Bjerregaard Stick, MSc
Department of Oncology, Rigshospitalet

Bo Nyhuus, MD
Department of Radiology, Rigshospitalet

Peter Nørgaard Larsen, MD
Department of Surgery, Rigshospitalet

Nicolai Aagaard Schultz, MD
Department of Surgery, Rigshospitalet

Place of investigation

Department of Oncology, Rigshospitalet
Blegdamsvej 9, 2100 Copenhagen

1. Background

Patients with colorectal cancer frequently presents with oligo metastases. 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. In these cases, patients can be considered for 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.

In most European countries MW-ablation is used when resection is not preferred, 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 MW-ablation in patients with colorectal liver metastases sized ≤4.0 cm found eligible for 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 Outcome Measure:

1. Freedom from local lesion progression analyzed on patient-level:
   - Defined as the time from randomization to local progression
   - Censoring: death from any cause, last follow-up
   - No censoring on disease progression outside of the treated lesions

Secondary Outcome Measures:

2. Overall survival:
   - Defined as the time from randomization to death from any cause
   - Censoring: last follow-up
3. Freedom from local lesion progression analyzed on lesion-level:
   - Defined as the time from randomization to local progression
   - Censoring: death from any cause, last follow-up
   - No censoring on disease progression outside of the treated lesions
4. ≥ grade 3 liver toxicity potentially associated with the treatment:
   - Defined as the time from randomization to first ≥ grade 3 toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
   - Censoring: death from any cause, last follow-up
5. Liver toxicity profile as descriptive statistics using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0
6. Quality of life as descriptive statistics using EORTC QLQ-C30

Details relating to freedom from local lesion progression outcomes

Local lesion progression is defined as >20% increase in the longest diameter and minimum 5 mm increase talking as reference the smallest longest diameter recorded since the treatment started in any of the treated lesions.

New lesions in the liver or recurrence of previously treated lesions in the liver are denoted regional lesions and does not lead to censoring.

Extrahepatic disease does not lead to censoring

The primary outcome measure will be analyzed on patient-level and the freedom from local lesion progression outcome in the secondary outcome measures will be analyzed on lesion-level.

Assessment of a potential impact of lesion size will be performed for the primary endpoint by a preplanned subgroup analysis between lesions <3 cm and lesions >= 3 cm. Hazard ratios in the two subgroups will be presented in a forest plot and a test for heterogeneity will be used to assess if the lesion size is predictive of treatment effect.

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 or open surgical 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 is a procedure using microwaves to heat tumor tissue thereby killing the tumor cells. MW-ablation can be performed either percutaneously or if percutaneous approach not is possible, by open surgery. Guided by ultrasound a thin needle is introduced through the skin into the tumor by the percutaneous approach or directly through the liver into the tumor during laparotomy. 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 (1, 3, 9, 12, 18, 24, 36, 48, 60 months 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 sometimes experiences influenza-like symptoms. The risks in relation to the procedure include bleeding, lesions of major bile ducts, perforation of the intestine and other adjacent structures. These complications are rare, below 5%.
If open approach by laparotomy is necessary, there is a 10-15 % risk of wound dehiscence and/or infection 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 server 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

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