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Statistical analysis plan v2

Protocol v2.2

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

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Approved by The Committee on Health Research Ethics in the Capital Region of Denmark

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1. Study Description

Brief Summary: This study is a randomized phase II trial between microwave ablation (MWA) and stereotactic body radiotherapy (SBRT) – two standard treatment modalities for colorectal patients with metastatic disease in the liver. Primary endpoint is freedom form local lesion progression.

Condition or disease: Colorectal Carcinoma, Liver Metastases

Intervention/treatment: Procedure: MWA or SBRT

Phase: phase 2

Detailed Description: Colorectal cancer patients with 1-3 liver metastases (diameter ≤4.0 cm) found unsuitable for resection are randomized 1:1 to either MWA or SBRT using SealedEnvelope. Chemotherapy is allowed. Curative treatment of extrahepatic disease must be initiated in patients with lung metastases and/or primary tumors. Patients will be analyzed according to the intention-to-treat principle. Data is captured in REDCap.

Purposes

1. To investigate SBRT as an alternative to 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

Hypothesis: 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. Study Design

Study Type: Interventional (Clinical Trial)

Estimated Enrollment: 100 participants

Allocation: Randomized using *Sealed Envelope*

Intervention Model: Parallel Assignment

Masking: None (Open Label)

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Primary Purpose: treatment

Study Start Date: July 25, 2018

Estimated Primary Completion Date: July 2022

Estimated Study Completion Date: July 2022

Stratification: Randomization will be stratified for treating center.

3. Arms and Interventions

Arm A: MWA
Intervention/treatment: Percutaneous ultrasound-guided MWA or open surgery MWA. The patient is fully anesthetized during the treatment.

Arm B: SBRT
Intervention/treatment: 3 fractions of 15 Gy (in total 45 Gy), 3 fractions per week. The dose is prescribed to the PTV encompassing 67% isodose. The SBRT plan is normalized such that the mean dose to the GTV is 100% = 67.5 Gy.

4. Outcome Measures

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.

Assessment of a potential impact of percutaneous MWA vs open surgical MWA will be performed for the primary endpoint and overall survival by a preplanned subgroup analysis.

5. Eligibility Criteria

Ages Eligible for Study: 18 years and older

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Inclusion Criteria:

- 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

- The multidisciplinary team should all agree that both percutaneous and open surgical MW-ablation and SBRT are safe as first treatment choice for the individual patient.
- Tumor sizes ≤4.0 cm
- Age ≥ 18 years
- Signed informed consent

Exclusion criteria:

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

6. 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

7. Sample size calculation

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:

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% in a superiority design. 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 with 161 patients [Jackson et al. IJROBP 2018].

8. Statistical considerations

Outcome measures are defined in section 4.

Freedom from local progression, overall survival and ≥ grade 3 liver toxicity will be evaluated by Kaplan-Meier estimator. Log rank statistics will be used to test for differences in freedom from local progression, overall survival and ≥ grade 3 liver toxicity between the two groups. p-values less than 0.05 will be considered significant. All Kaplan-Meier plots will contain confidence bands and the number of patients at risk at regular intervals using the statistical package R. Data will be analyzed by the intention to treat principle.

Data analysis is scheduled one year after last patient is randomized. Timing of outcome assessments described in main protocol.

Descriptive statistics and explorative analyses of liver toxicities and quality of life will be performed.