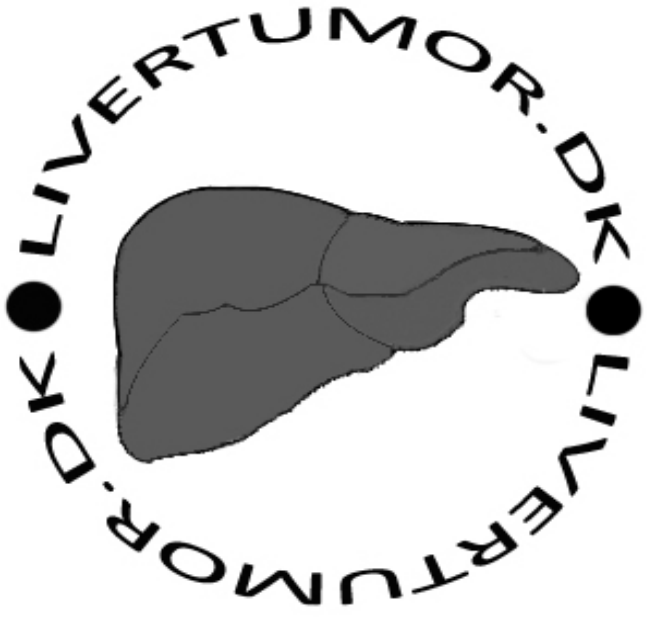
The International Liver Tumor Group

RAS-trial

Radiofrequency ablation versus stereotactic body radiation therapy for colorectal liver metastases: A randomized trial



Version 10: September, 2009

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SYNOPSIS

Radiofrequency ablation versus stereotactic body radiation therapy for colorectal liver metastases: A randomized trial

1. Background

Large retrospective studies on surgical resection of liver metastases from colorectal cancer (CRC) have demonstrated 5-year survival rates of 25-40%. The survival depends upon patient and tumor characteristics, but long-term survival is seen even in some patients with very poor prognostic factors. However, only a minor fraction of the patients with CRC liver metastases are suitable for resection due to technical criteria or the presence of concomitant diseases.
The efficacy of radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) in the treatment of CRC liver metastases is tested in the present randomized phase III trial

2. Hypothesis

One of the two treatments has a local tumor control rate which is 10% better than the other after a median follow up of 3 years.

3. End-points

Primary endpoints:	Local progression-free survival by patient based analysis after 3 years
Secondary endpoints:	Toxicity (primarily based on CTCAE v. 3.0) Overall survival after 3 years Progression (local or distant) free survival after 3 years Local control on tumor based analysis after 3 years Treatments given for local or distant progression after study treatment Quality of life 0, 1, 3, 6, 12, 24, and 36 months after treatment

4. Design

Multi-centre randomized phase III trial. Patients with CRC liver metastases not suitable for surgical resection will be randomized between RFA and SBRT. Randomization will take place in a centralized data centre. A total number of 300 patients are required.

5. Inclusion criteria

1. Adenocarcinoma of the colon or rectum with liver metastases verified by radiological (CT- or MRI) or histological/cytological examination. Only in case of a solitary metastasis smaller that 10 mm, a biopsy from liver metastasis is compulsory.
2. Metastases must be visible both on diagnostic- and dose planning CT scans. In centres using ultrasonography for guidance of RFA, the tumours should also be visible by ultasonography.
3. The patient should not be suitable for surgical resection due to technical or patient related circumstances. Resectability must be judged by a trained hepatobiliary surgeon and discussed in a multidisciplinary team meeting.
4. Previous surgical resection, LITT, cryotherapy, RFA is allowed.
5. Karnofsky performance status $\geq$70.
6. Presence of 1-4 metastases.
7. Diameter of largest metastasis maximum 40 mm.

8. All tumors should be feasible for treatment with each of the two modalities, RFA and SBRT.
9. Age over 18 years at time of inclusion.
10. Signed written informed consent obtained.
11. Adequate liver function as defined by bilirubin<3mg/dl, alb>2.5g/dl, normal PT, PTT except if the patient uses anticoagulants and liver enzymes less than 3 times upper limit of normal. Renal function should be sufficient to allow iv. contrast for CT-scanning according to the local policy.
12. Adequate bone marrow function: Hbg≥8 g/dl, platelets≥100.000 and leucocytes≥ 2.000/ml

6. Exclusion criteria
    1. Extrahepatic malignant disease. However, patients with lung metastases treated with a R0 resection or by RFA or SBRT and without evidence of local progression may be included.
    2. Uncontrolled primary tumor.
    3. Inaccessibility for treatment and follow up.
    4. Pregnancy.
    5. Prior malignancy within the last five years (except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the skin or in situ carcinoma of the cervix, surgically cured), or localized prostate cancer without evidence of biochemical progression.
    6. Previous inclusion in this study.
    7. Liver cirrhosis (any Child-Pugh grade), active hepatitis or presence of ascites.
    8. Previous radiotherapy to the liver.
    9. Chemotherapy or biological targeted drug within 4 weeks.

7. Treatment

RFA: Treatment should be given with a standard RFA-system, which allows an ablation margin of at least 5 mm around the tumor. Percutanous as well as open and laparoscopic techniques are allowed.

SBRT: Treatment must be given with a stereotactic technique, allowing the use of a tight CTV-to-PTV margin, also for tumors with extensive respiratory motion.

Treatment schedule is 3 fractions of 12.50 or 13.75 or 15.00 or 16.75 Gy. The highest dose that meet the dose-volume constraints should be used. Dose prescription is at the 67% isodose surface that should tightly enclose the PTV surface. The dose to the PTV should be the highest possible dose level that on the same time fulfils the dose constraints of the OAR. Each isocenter should be treated within 8 days and each fraction should be given with a minimum time interval of 40 hours.

Chemotherapy or biological targeted therapy (systemic or hepatic artery infusion) before or after RFA/SBRT is accepted. Minimum interval between chemotherapy or biological targeted therapy and inclusion into the study should be at least 4 weeks. Systemic antineoplastic treatment should not be started within another 4 weeks after SBRT/RFA. Type and schedule of chemotherapy should be according to choice of the participating institution, but patients in the two arms should be treated by similar policy.

Re-treatment and treatment of new metastases is allowed and should be performed based on local policy.

8. Evaluation before randomization
    - A medical history, physical examination, weight, assessment of Karnofsky performance status within 4 weeks prior to study entry.
    - Evaluation by an experienced liver surgeon (discussed on a multidisciplinary team meeting) within 6 weeks prior to study entry.
    - CT scan (with intravenous contrast) to include lungs, the mediastinum, liver, and abdomen within 4 weeks before inclusion. Primary tumor dimension will be measured by CT.
    - Ultrasound of liver within 4 weeks before inclusion.
    - Blood test: INR, PT, PTT, AST, ALT, total bilirubin, albumine, alkaline phosphatase, creatinin, hb, platelets, leucocytes, CEA within 4 weeks before inclusion.

9. Evaluation before treatment
    - CTCAE v. 3.0 toxicity grading system.
    - Quality of life questionnaire.
    - Whole body FDG PET/CT or PET scan are optional.
    - MRI of the liver is optional.

10. Evaluation after treatment
    - A medical history, physical examination weight, assessment of Karnofsky performance status and CTCAE v. 3.0 toxicity score 1, 3, 6, 9, 12, 18, 24 and 36 months after start of treatment.
    - CT scan with intravenous contrast to include lungs, mediastinum, liver and abdomen 3, 6, 9, 12, 18, 24 and 36 months after start of treatment or until occurrence of local or distant progression. A contrast enhanced CT-scan including the liver should always be performed at the time a recurrence is discovered. Typical recurrences do not have to be biopsied (see page 14). However, biopsies should be performed in case of any atypical appearance that could represent a recurrence. A participating centre can decide that FDG-PET/CT replaces CT and a MRI can replace CT of the liver.
    - Whole body FDG PET/CT or PET scan 3 and 12 months after treatment (optional).
    - Quality of life questionnaire (1, 3, 6, 12, 24, and 36 months after treatment).
    - Blood test at 1, 3, 6, 9, 12, 18, 24, 36 months, including AST, ALT, total bilirubin, albumine, alkaline phosphatase, creatinin, hb, platelets, leucocytes, INR, CEA.

11. Statistical considerations

Total number of patients included in the trial is 300. Minimum follow up time is 18 months. Survival analysis should be based on intention to treat principle.

Stratification according to centre will be performed at randomization. In case of imbalance, an adjustment for the following confounders will be performed in the final analysis:

1. Diameter of largest metastasis (smaller or larger than 30 mm)
2. Number of metastases (1 or $\geq$2)
3. Chemotherapy after discovery of metastases (no or yes).
4. Previous liver resection, RFA, cryotherapy, or LITT (no or yes)
5. Planned RFA approach (as determined before randomization): percutaneus versus intraoperative or laparoscopic
6. Radiotherapy dose level

FLOW SHEET

Time	Action	Comments
Before inclusion	CT-scan (thorax & abdomen)	4 weeks before randomization
	Ultrasound of liver	4 weeks before randomization
	Medical history, physical examination, weight, Kanowsky performance status	4 weeks before randomization
	Blood tests: INR, PT, PTT, AST, ALT, total bilirubin, albumine, alkaline phosphatase, creatinin, hb, platelets, leucocytes, CEA	4 weeks before randomization
	Multidisciplinary evaluation	6 weeks before randomization

	Action					
	Med.hist. & phys. ex.	CTthorax+abdomen*	Toxicity	Blood tests **	QoL	PET/CT ***
After randomization, but before treatment			X		X	X optional
Follow up 1 month	X	X	X	X	X	
Follow up 3 months	X	X	X	X	X	X
Follow up 6 months	X	X	X	X	X	
Follow up 9 months	X	X	X	X		
Follow up 12 months	X	X	X	X	X	X
Follow up 18 months	X	X	X	X		
Follow up 24 months	X	X	X	X	X	
Follow up 36 months	X	X	X	X	X	

2 INTRODUCTION

Unlike most other cancers, CRC frequently presents with solitary or oligo-metastases and often the liver is the only involved site. This has led to an aggressive surgical approach in the treatment of these patients. Long term results from retrospective analysis of patients treated with resection of CRC liver metastases show 5-year overall survival rates of approximately 30% and even some patients with very poor prognostic factors will become long term survivors [1, 2]. Surgical limitations are most frequently related to the volume of residual liver after the procedure rather than to classical prognostic factors such as number and size of metastases [3]. Even though it is possible to perform extensive resection of the liver and the lung with removal of as much as 80% or 50% of the organs, respectively, the percentage of patients that are amendable for resection is most often only in the range of 10-25% . Exclusion criteria for surgery include number, size, localization of the metastases in the liver, coexisting liver dysfunction or co-morbidity. There is therefore a great demand for other local treatments for patients with CRC metastases. Non-surgical ablation methods such as cryotherapy, laser-induced interstitial thermotherapy (LITT) and radiofrequency ablation (RFA) with the latter being the presently most frequently used method, have been evaluated primarily in retrospective studies. In the recent years, SBRT has been introduced as a non-invasive method for ablation of liver metastases. The present randomized phase III study is designed to compare the efficacy of RFA and SBRT in the treatment of CRC liver metastases.

Especially metastases larger than 30 mm pose a problem in non-surgical treatments for liver metastases. Patients with large liver metastases have poor outcome compared to those with smaller tumor size[4-6]. A study has shown that patients treated by RFA prior to chemotherapy have better survival than patients treated wit opposite schedule [7]. However, the implication of chemotherapy in relation to local treatment of liver metastases is unclear.

2.1 RFA

RFA is presently the most widely used non-surgical method for ablation of liver metastases when resection is not possible. The method is often used in combination with resection in an ”open” procedure. Percutaneous RFA is a minimal invasive technique in which the radiofrequency probe guided by ultrasound or by a CT fluoroscopy is placed in the tumour centre. Ablations up to 7 cm are possible. A common cause of failure after RFA is the inhomogeneous heating of tissue due to cooling effect by blood vessels and improper placement of the needle. An ablation margin of more than 5 mm around the tumour is preferred.

Local recurrence rates of 44.4% at 18 months were reported by Solbiati *et al.* for CR metastases with a median of 2.6 cm of diameter[8]. For tumors greater than 4cm the local recurrence rate was 68%.

Pawlik *et al.* found that failure at RFA treated sites for liver metastases was uncommon, with a rate of only 2.3% for tumors with a median size of <2cm[9].

Wood *et al.* presented a 6.5% local recurrence rate associated to RFA for intrahepatic malignancies ≤3cm size. For tumors larger than 3 cm, the failure rate was 33%[10].

Laparoscopic or intraoperative RFA may result in a higher rate of local control compared to the percutaneous technique due to improved imaging by the laparoscopic/intraoperative technique [11].

Unpublished data from Erasmus Medical Centre also indicates that laparoscopic approach is superior to percutaneous technique. RFA was used to treat a total of 90 tumours with a maximal diameter of 3 cm in 57 patients with a primary or secondary hepatic malignancy. A local recurrence occurred in 7 out of 31 tumors (23%) treated percutaneously under ultrasound guidance. In contrast, only 4 out of 59 tumours (7%) treated by RFA during laparotomy developed a recurrence during follow-up.

In studies on RFA by Abdalla *et al.* [12], Solbiati *et al.* [13] and Berber *et al.* [14], survival rates were 30-46% 3 years after treatment. Generally, large tumor size was the strongest prognostic parameter for recurrence or death whereas synchronous appearance, centrally located metastases and numbers of metastases had significant prognostic value in at least one of the studies. In a study by Sorensen, survival rate 3 years after RFA was 46%[15].

2.2 SBRT

SBRT is a non-invasive technique based on high-precision radiotherapy suitable for treatment of small targets in the body [16, 17]. The efficacy of SBRT has primarily been investigated in the treatment of limited stage non-small cell lung cancer [18-20].

Schefter *et al.* enrolled 16 patients with liver metastases in a phase I trial[21]. They demonstrated that it was possible to increase the radiation dose to 60 Gy (prescribed to the 80-90% isodose line) in 3 fractions without any dose limiting toxicity in patients with normal liver function. Kavanagh et al. have recently reported an update of this trial showing an actuarial local control rate of 93% at 18 months [22].

Herfarth et al. published results of a phase I-II trial including patients with liver metastases, colangiocarcinomas and hepatocellular carcinoma. The dose was increased from 14 to 26 Gy given as a single fraction [23]. Local control rate was 81% 18 months after treatment. In this study, only mild toxicity reactions were observed. In a later publication including also patients accrued after the phase I-II study was closed, a considerably lower control rate was reported. The poorer results were explained by a high representation of CRC liver metastases where the local control rate was 45% compared to 91% for metastases of other tumor types.

Mendez Romero *et al.* reported results of a phase I-II study including patients with liver metastases and hepatocellular carcinoma with normal as well as with impaired liver function (cirrhosis Child-Pugh A and B)[24]. Liver metastases, HCC without cirrhosis and HCC<4cm with cirrhosis, received a dose of 37.5 Gy (prescribed at the 65% isodose) in 3 fractions. HCC $\geq$ 4cm in the presence of cirrhosis received 25-30 Gy in 3-5 fractions. One possible treatment related death after hepatic failure occurred in a Child-Pugh B patient. This patient was treated with 30 Gy in 3 fractions. Two patients with liver metastases developed toxicity grade 3 based on an increase of GGT, one asymptomatic and another with asthenia grade 2. Actuarial local control was 94 and 82% after 1 and 2 years, respectively.

Hoyer *et al*. has published results of a Danish phase II study of CRC metastases primarily located in the liver treated with a central dose of 45 Gy at the isocenter, delivered in three fractions[25]. One out of 64 patients developed a possible radiation induced liver disease (RILD) resulting in death. Two patients developed duodenal ulcerations and one patient a colonic ulceration. Despite these, only moderate or mild toxicity was observed. Local control rates after 1 and 2 years were 89 and 79%.

Since a large proportion of the patients had more than 1 metastasis, individual patient based local control rate at 2 years was 64%. Survival rates in these patients who were deemed inoperable were 22 and 13% at 3- and 5-years after treatment which are comparable to survival rates of patients with poor prognostic factors after surgical resection.

Wulf *et al*. demonstrated in a phase I-II study, including liver metastases and one cholangiocarcinoma, a local control rate of 76% and 61% at 1 and 2 years after SBRT. Patients were mostly treated with 30 Gy in 3 fractions [26]. In a recent publication including patients treated with a higher dose of 37.5 Gy in 3 fractions (65% isodose) or 26 Gy in one fraction (80% isodose) the actuarial local control observed was 92% and 66% at 1 and 2 years, respectively [27]. High radiation dose was the only significant factor for local control in a multivariate analysis.

3 STUDY DESIGN

Multi-centre randomized phase III trial. Patients with non-resectable CRC liver metastases will be randomized (1:1) between RFA and SBRT. Randomization will take place in a centralized data centre. The primary endpoint is local progression-free survival in patient based analysis after a median follow up of 3 years. No stratification will be performed in the randomization procedure. However, in case of imbalance of prognostic factors an adjustment based on confounding factors may be performed.

4 STUDY POPULATION

4.1 Inclusion criteria

Patients included into the study should fulfil the following criteria:

1. Histological proven adenocarcinoma of the colon or rectum with radiological (by CT- or MRI) or histological-/cytological verified liver metastases. Only in case of a solitary metastasis smaller that 10 mm, a biopsy from liver metastasis is compulsory.
2. Metastases must be visible on diagnostic- and dose planning CT scans. In centers using ultrasonography guided RFA, the tumours should also be visible on ultrasonography.
3. The patient should not be suitable for surgical resection due to technical or patient related circumstances. Resectability must be judged by a trained hepatobiliary surgeon and discussed in a multidisciplinary team meeting.
4. Previous surgical resection, LITT, cryotherapy or RFA treatment of liver metastases is allowed.
5. Karnofsky performance status $\geq$70.
6. Presence of 1-4 metastases.
7. Diameter of largest metastasis should be 40 mm.
8. All tumors should be feasible for treatment with each of the two modalities, RFA and SBRT.
9. Age over 18 years at time of inclusion.
10. Signed written informed consent obtained.
11. Adequate liver function: bilirubin<3mg/dl, alb>2.5g/dl, normal PT/PTT except if the patient uses anticoagulants, liver enzymes<3 times upper limit of normal. Renal function must be adequate for infusion of iv. contrast for CT-scan according to the local policy.

12. Adequate bone marrow function: Hbg≥8 g/dl, platelets≥100.000 and leucocytes ≥2.000/ml

4.2 Exclusion criteria

Patients included into the study should not have any of the following criteria:

1. Extrahepatic malignant disease. However, patients with lung metastases treated with a R0 resection or by RFA or SBRT and without evidence of local progression may be included.
2. Uncontrolled primary tumor.
3. Inaccessibility for treatment and follow up.
4. Pregnancy.
5. Prior malignancy within the last five years (except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the skin or in situ carcinoma of the cervix, surgically cured), or localized prostate cancer without evidence of biochemical progression.
6. Previous inclusion in this study.
7. Undelying liver cirrhosis (any Child-Pugh grade), hepatitis or presence of ascites
8. Prior radiotherapy to the liver.

5 INVESTIGATIONS BEFORE TREATMENT

Examinations before randomization

1. Medical history, physical examination, weight and assessment of Karnofsky performance status within 4 weeks prior to study entry.
2. Evaluation of a contrast enhanced CT scan of the abdomen by an experienced liver surgeon within 6 weeks before inclusion.
3. CT scan with intravenous contrast to include lungs, mediastinum, liver, and abdomen within 4 weeks before inclusion. Primary tumor dimension will be measured on CT.
4. Ultrasound of the liver within 4 weeks before inclusion.
5. Blood test: PT, PTT, AST, ALT, total bilirubin, albumin, alkaline phosphatase, hbg, platelets, leucocytes, creatinin, CEA within 4 weeks before inclusion.

Examination before treatment

1. CTCAE v. 3.0 toxicity grading.
2. Quality of life questionnaires: Euro QoL-5D, Euro QoL- VAS, QLQ-C30 and QLQ-LM21 (in countries where authorized translation is available).
3. Whole body FDG PET/CT or PET scan (optional).
4. MRI of the liver (optional).

MRI, FDG PET and FDG PET/CT are optional in both arms. However, if an institution prefers to use one of these methods, it should be used in patients allocated to both study arms and it should be performed after randomization. The PET/CT and/or MRI may be used for SBRT treatment planning.

6 TREATMENT

Patients with technical inoperable CRC liver metastases are randomized between

- Arm A: RFA guided by ultrasonography or computer tomography of all visible tumors securing a necrosis area covering the macroscopic tumor and a margin of at least 5 mm.
- Arm B: SBRT of all visible tumors to a dose of 3 x 12.50 or 13.75 or 15.00 or 16.75 Gy at the periphery (67% isodose) within 8 days (for each target). The dose to the PTV should be the highest possible dose level that on the same time fulfils the dose constraints of the OAR. The applied tight CTV-to-PTV margin to guarantee adequate tumor coverage has to be consistent with the selected stereotactic approach.

Treatments in the two arms are described in details in paragraph 19.0.
The treatment should be initiated within 4 weeks after randomization.

7 HYPOTHESIS

Both treatments, RFA and SBRT are considered experimental. Neither of the treatments has been tested in randomized trials. The basic hypothesis is that one of the treatments has a local control rate which is 10% better than the other after 3 years in this randomized phase III study.

7.1 Primary endpoint

Primary end-point is local progression-free survival after a median follow up time of 3 years. A local failure is claimed when there is viable tumor tissue within or adjacent to a treated tumor volume detected after study treatment.

Typical local recurrences on follow up CT with iv contrast or MRI after RFA are hypodense tumors after i.v. contrast.expanding either within or adjacent to the RFA necrosis.

Typical recurrences after SBRT on follow up CT are expanding either within or adjacent to the original treated tumor. An increase of more than 25% in tumor area on a CT-scan of a treated tumor (multiplied orthogonal diameters) is suspicious for recurrence.

If a new nodulus is separated with 5 mm or more from the treated tumor, the new tumor is considered a new metastasis and not a local recurrence.

If there is a suspicion of local progression at follow-up scans, a biopsy should be taken. Alternatively, an MRI may be performed. If no conclusion can be withdrawn, a second CT/MRI with at least 8 weeks apart is needed to confirm the progression. Enhanced FDG-PET in a previously treated tumor is not by itself sufficient to confirm a recurrence. A recurrence can only be claimed if the co-registered CT shows atypical regrowing tumor

Biopsies are not required in typical new lesions visible on CT- or MRI scans. However, biopsies should be taken from atypical lesions.

A patient treated for more than one metastasis will be considered having local failure if failure occurs in one of the tumors, even if the other treated tumors still are controlled.

A patient should be followed up for local control until 3 years after treatment or until local or distant failure is detected. Afterwards, the patients are only followed-up for SAE (section 9), type of anticancer treatment and survival.

The patient is considered *off-study* in case of local or distant failure, after 3 years of follow up or when the study is closed. The study will be closed 18 months after inclusion of the last patient and analysis will be performed thereafter.

If major violation according to inclusion and exclusion criteria occurs, the patient should be excluded from the analysis. Patient who are deemed not-treatable after randomization based on treatment planning PET/CT- or CT-scans or based on intraoperative procedures will remain in the analysis and analysed according to the "intention to treat principle" as mentioned in the paragraphs 18.1.1 and 18.2.4.Ok

7.2 Secondary endpoints

Progression free survival (combined local and distant progression), overall survival, local control on tumor based analysis, treatments given for failure after study-treatment, acute toxicity, late toxicity, quality of life are secondary endpoints in this trial. Progressive disease is defined as local recurrence or development of a new hepatic or extrahepatic metastasis.
Toxicity should be graded by means of the CTCAE v. 3.0 grading system (https://webapps.ctep.nci.nih.gov/webobjs/ctc/webhelp/welcome_to_ctcae.htm). Questions concerning toxicity related to the liver and biliary system will be added. Toxicity grading will be performed before and at each follow-up visits after treatment.
Quality of life evaluation is important in patients with metastatic disease with limited expected life time and who are offered a treatment that potentially interferes with their quality of life. Quality of life will be tested by the two generic questionnaires, Euro QoL-5D, Euro QoL- VAS, and the cancer specific QLQ-C30. The colorectal liver metastases module, QLQ-LMC21, will be recommended on the available translated languages (Dutch, English, French and Italian and Danish and Swedish when available). The patients will be asked to fill in questionnaires before and at 1, 3, 6, 12, 24 and 36 months after treatment.
When the patient is off study – as mentioned in paragraph 8.1 – they will only be followed for treatment related SAE, secondary cancer treatment and survival.

7.3 Biological studies

Optional translational studies on biological and hypoxic markers

8 FOLLOW UP

Evaluation after treatment

- A medical history, physical examination weight, assessment of Karnofsky performance status and CTCAE v. 3.0 toxicity score 1, 3, 6, 9, 12, 18, 24 and 36 months after start of treatment.
- CT scan with intravenous contrast to include lungs, mediastinum, liver and abdomen 1, 3, 6, 9, 12, 18, 24 and 36 months after start of treatment or until occurrence of local or distant progression. Biopsies should be performed in case of any atypical appearance that could represent a recurrence. A participating centre can decide that FDG-PET/CT replaces CT or if a MRI should replace CT of the liver. However, if the CT is replaced by other imaging, this should be the case for patients in both study arms and PET/CT should always be acquired with contrast enhancement.

- Whole body FDG PET/CT or PET scan 3 and 12 months after treatment (optional). MRI can replace CT of liver, but it should be combined with CT of lungs, mediastinum and abdomen. This combination (without iv. contrast) can be used in case of allergy to iv. contrast.
- Quality of life questionnaire 1, 3, 6, 12, 24, and 36 months after treatment.
- Blood test at 1, 3, 6, 9, 12, 18, 24, 36 months, including AST, ALT, total bilirubin, albumine, alkaline phosphatase, creatinin, hb, platelets, leucocytes, INR, CEA.

9 SERIOUS ADVERSE EVENT (SAE)

Any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly/birth defect or is a medical important event is considered serious adverse event (SAE). SAE's should be reported to the study centre within 24 hours after its occurrence.
All SAE (related and unrelated to treatment) within 30 days after treatment should be reported. After that only SAE considered related to the study treatment should be reported.

10 ETICS CONSIDERATIONS

The Helsinki Declaration

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

It is the responsibility of the Investigator to obtain approval of the Study Protocol from the Ethics Committee and to keep that committee informed of any Serious Adverse Events and Serious Device Effects and amendments to the protocol.

Patient information and consent

It is the responsibility of the Investigator, to provide each patient (or the patient's legally authorized representative), prior to that patient's participation in the study, with complete and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. Written patient information (included as an appendix to the protocol) should be given to each patient before enrollment. It is the responsibility of the Investigator to obtain signed informed consent from all patients prior to their inclusion in the study. The signed Informed Consent forms should be filled by the Investigator and archived for possible future audits. The Investigator will confirm the receipt of an informed consent form from each patient by signing the appropriate page of the Case Report Form. It should be noted on the Patient Record that the patient is taking part in a clinical study.

Patient data protection

The patients will be identified in the CRF by patient number and initials.

The Investigator should keep a patient identification list, including sufficient information to link records, i.e. CRF and hospital records.

The patients should be informed that the data will be stored and analyzed by computer, that national and local regulations for the handling of computerized data will be followed, and that only the Investigator will be able to identify individual patient data.

11 CASE REPORT FORM

See Appendix.
Each center will submit data via the data entry module on the trial web-site (www.livertumor.dk). Copies of the case report forms (CRFs) should be mailed to the Study Center. A signed *inclusion form* should be faxed within 14 days after inclusion (FAX: +4586197109). Other CRFs should be mailed by surface mail on request from the Study Center.
For SBRT patients, dose volume histograms (DVH) of targets and organs at risk (OAR) should be submitted by e-mail after completion of treatment or by request from the Study Center.

12 MONITORING

A study monitor will visit the study site during the study as agreed by the Investigators. The monitor will ensure that the protocol is followed, that results are recorded, that Adverse Events are reported, and record keeping is satisfactory. In addition, there will be verification that clinical facilities remain accurate, and that the Case Report Forms are in agreement with source data. In addition, the monitor or the QA-group should be allowed access for monitoring of the quality of the technical / physics aspects of the treatments and to schedule visits at the participating centers. For this purpose, the monitor will be given access to hospital records, original laboratory data etc., as far as these relate to the study, without jeopardizing patient integrity, and as agreed with the Investigator prior to the study. CRFs for all included patients will be made available to the monitor for review and collection as agreed with the Investigator.

13 STATISTICAL CONSIDERATIONS

Primary end-point is local progression free survival after a median follow up of 3 years after treatment. Most frequently local control rates are around 80% at 2-3 years after treatment. Since most patients are expected to have 1 or 2 metastases the individual based local control rates are expected to be between 80% and 64%. For power analysis, an individual local control rate of 75% is assumed.
To show a significant difference with a two sided test where alpha = 0.05 and 80% power, assuming local control probability of 75% in one of the arms and the other arm being 10% better, a number of 150 patients per arm (total: 300) is required. The analysis should be two-sided. With an estimated inclusion rate of 75 patients per year, the inclusion time is expected to be 3 years.
Analysis of local control as the primary end-point will be performed on a patient based analysis. This means that a patient with more than one treated tumor is considered having a local failure if a failure is observed in one tumor, even if the other tumors are still controlled. As a secondary end-point, local control will be analysed by tumor based analysis.
Stratification according to centre will be performed at time of randomization.
In case of imbalance of the following possible prognostic factors, an adjustment of confounders will be performed in the final analysis of the study:

1. Diameter of largest metastasis (smaller or larger than 30 mm)
2. Number of metastases (1 vs. $\geq$ 2)
3. Chemotherapy after occurrence of liver metastases (no or yes)
4. Previous liver resection, RFA, cryotherapy, LITT (no or yes)

5. Planned RFA approach (as determined before randomization): percutaneous versus intraoperative or laparoscopic

Analysis will be based on intention to treat principle.

14 RANDOMIZATION PROCEDURE

Patients are screened by scans and blood tests, which are considered standard of care for patients with liver CRC metastases. They will be informed by the investigator or by an appointed co-investigator at the treatment centre. Before patients agree to participate in this trial they will receive oral and written information. A "Patient information sheet" and a consent form, prepared in the local language will be handed to the patients. The formal consent form must be signed and dated by the patients and the investigator before patients are submitted to any study-specific procedure.
Patients that fulfil the eligibility criteria and who sign and date the formal consent will be randomized on-line on the study web site (www.livertumor.dk).
Questions concerning individual patients should be directed to the Principal Investigator (+4589492529 or +4589493333 [Morten Hoyer, Department of Oncology]).
The treatment should be initiated within four weeks after randomization.

15 TRIAL ORGANIZATION

A Study Group has the overall responsibility and rights to this trial. The Study Group consists of representatives from each participating site. All sites have the rights to be represented by a radiation oncologist, a radiologist, a hepato-biliary surgeon and a medical physicist.
A Protocol Group will take the responsibility of writing the study protocol, run a Study Coordinating Centre, monitor the trial and do the data analysis. A Technical Quality Assurance Group will take the responsibility of technical/physics quality assurance during the trial, under authority of the Protocol Group. The Primary Investigator is chairman of the Protocol Group and members of the Protocol Group are all members of the Study Group.

16 QUALITY ASSURANCE AND -CONTROL

The quality of the clinical recording will be assured by the Study Coordinating Centre (e.g., compliance to the clinical protocol, CRF, randomization, SAE reports, QoL reports, clinical data integrity).

Technical/physics quality assurance will be coordinated from the Technical Quality Assurance Centre (RAS@erasmusmc.nl). Before inclusion of the first patient, study centres should be credentialed. If necessary, assistance will be provided to successfully complete the process. During the trial the QA-centre will monitor the technical quality of treatments according to the protocol requirements (e.g., positioning, target definition, dosimetry, by remotely checking patient data submitted to the QA-centre, and by visiting treatment sites.

16.1 Credentialing

Facility questionnaire
A questionnaire will be sent out to all participating centres to document previous experience in SBRT of liver tumors, treatment team individuals, the treatment procedure, and the electronic data export formats.

Description of technical procedures (RT)
A document should be provided including a technical description of the complete treatment procedure (step-wise, from target definition to dose delivery) including a timeline of events. The document is intended to provide detailed insight in the technical/physical procedures that influence the quality of dose delivery. (e.g., measures to manage respiratory motion, day-to-day motion, positioning/registration procedures) It will be used to judge if the CTV-PTV margin prescription is consistent with the technical approach and to identify confounding factors.

The document should include:

- An introduction with a general overview of the treatment approach, as well as a brief description of previous experience of SBRT of liver tumors.
- Description of patient fixation
- Description of method to account for respiratory motions of the target
- Description of the GTV(=CTV) definition procedure. Imaging equipment (e.g., PET, MRI, CT), the settings used for this (e.g. slice distance, pulse sequence, rotation, speed e.c.t.) and the protocols (e.g. free-breathing, breath-hold, gated acquisition, 4D, cine-mode, contrast agent e.c.t.). If applicable, the procedure to compose the final GTV from the various sources.
- Description of CTV-PTV margin, as further explained below.
- Description of the dose planning procedure, including the planning technique (IMRT, conformal, arc, etc) planning system and the dose calculation algorithm.
- Description (detailed) of the methodology for geometrical verification.
- Description of treatment procedure

Description of QA-tests (RT)
A rationale for the CTV-to-PTV margin should be provided supported by a quantitative overview of geometrical inaccuracies. All tests performed in-house that identify the sources and magnitudes of geometrical inaccuracies to support this claim should be documented, including their results. These could include retrospective tests based on a material of a group of treated patients. Test results adopted from other centres, product vendors, or from the literature should be included with a reference. The document will be reviewed by the QA-group to verify the CTV-PTV margin used, or if margins are considered inadequate, for the purpose of the trial, to recommend other margins.

Tests that may be used to verify the geometrical accuracy are:

- coincidence of planning and delivery iso-center (e.g., Winston-Lutz)
- routines to check room-lasers used in the set-up
- reproducibility and effectiveness of respiratory control measures
- coincidence of planned and delivered dose
- patient position verification (e.g., portal imaging, external marker localization)
- image-based delivery control (IGRT) correcting for daily changes (cone beam CT, in room KV, in room CT, other CT)
- position/shape reproducibility of anatomic structures
- reproducibility in target contouring

Planning and contouring exercise

CT-scans will be sent out to each center to perform exercises on tumor definition and dose planning. Results will be submitted to the QA-center. which will check consistency among the participating centers. The tests should be completed before inclusion of patients in the study.

Two tests will be scheduled:

- GTV contouring exersice. A venous phase contrast enhanced CT-scan will be provided to delineate the CTV. The tumor should be contoured in accordance to section 18.2.1 and 18.2.2.
- Dose planning exersice. A large volume planning CT-scan will be provided in which the PTV and GTV volumes have been defined. A dose plan is to be constructed according to the protocol specifications and the prescibed iso-dose level.

Finished exersices should be submitted to the QA-center using formats described in section *protocol monitoring*.

16.2 Protocol monitoring

The technical quality of treatments will be remotely monitored by the QA-center which will review the data related to the treatment of each patient, as specified below. The electronic data will be submitted to the internet server of the QA-center, for which the patient will be identified equivalent to the identification used in the CRF. Additionally, site visits can be scheduled to review the implementation of a treatment procedure and or to provide assistance. Electronic data and forms will be submitted to the internet server of the QA-center (ftp.erasmusmc.nl). Futher directions will be provided to all study centres. Any request for assistance can be directed to: RAS@erasmusmc.nl.

RT

Once a patient's treatment has been accomplished, no later than two weeks after treatment completion the following treatment data must be submitted to the QA-center:

- The complete treatment plan including: volumetric data used for initial target definition including contours (e.g., contrast enhanced CT-scans), planning CT-scan, beam configuration, all contours used for target definition, all OAR contours, , the volumetric dose distribution, and DVHs of CTV, PTV, OARs. These data should be exported from the treatment planning system in DICOM RT formats (RT struct, RT dose, RT plan), unless otherwise agreed upon with the QA-center.

RFA

The RFA treatment protocol must follow the standard company protocols of the different generators used (Valleylab /Radionics cooled tip system, RITA system or Radiotherapeutics system)
The following treatment data must be submitted to the QA-centre:

- Pre-operative CT and directly post-operative CT

17 PUBLICATION POLICY

The main results of the present trial will be presented in international meetings and medical journals. Before presentation, the results will be presented to the members of the Study Group who will have the rights to make their comments.

First authors of the papers will be the members of the Protocol Group followed by those who have included the highest number of patients into the trial. Members of the Study Group who have been active in this trial and their affiliation will be mentioned in an Appendix.
Any spin of study of this trial can be published by those who participate in these studies. However, the present trial should always be mentioned as the RAS-trial by the International Liver Tumor Group and the Study Group should always be informed and have the right to make comments prior to publication.

18 TREATMENT SPECIFICATIONS

18.1 Radiofrequency ablation

RFA is the presently most widely used non-surgical method for ablation of liver metastases when resection is not possible.
There are different manufactures of RF-generators with a variety of electrodes. The three most important systems are: Cooled-tip RF ablation system (Valleylab, Tyco), RITA RF-ablation system (RITA medical, Angiodynamics) and RF 3000® RF-ablation system (Boston Scientific). All generators and electrodes have their own ablation protocol for the different ablation sizes. Each centre may choose its own system. However, if other than above mentioned systems are used, it should be reported and approved by the RFA-quality assurance group. The system used for RFA in each patient should be recorded in the CRF. Company protocols must be used for RF-ablation.

18.1.1 Intraoperative, laparoscopic or percutaneous RFA

RFA can either be performed as an open procedure (laparotomy), guided by laparoscopy or percutaneously. They can all be guided by ultrasound and the percutaneous method can also be guided by CT fluoroscopy. Before randomisation, the team will take the decision whether the tumour will be treated with RFA in an open procedure/laparoscopic or percutaneous and the patient will be stratified accordingly. If new lesions are discovered during the procedure they will, if possible, be treated in the same session. If new findings during the treatment session makes RFA meaningless the patient will still be analysed according to the the “intention to treat principle”. An example could be that peritoneal carcinomatosis was discovered,

18.1.2 Number and size of necroses

A maximum of 4 tumors each with a maximum diameter no more than 4 cm can be treated. The radiologist should aim to create a necrosis covering the tumor with a margin of at least 0.5 cm. If additional intrahepatic tumors are found during the RFA procedure, they may be treated as well and the patient will remain eligible for analysis. However, if the total number of metastases exceeds 4, the patient should be withdrawn from the study and can be treated according to local policy.

18.1.3 Recording and reporting

The following information related to the RFA-procedure shall be recorded in the CRF:

1. Number of treated tumors and their lobe-localization, individual size measured on the scan used for guidance (UL or CT).
2. Distance from vena cava, pedicle, duodenum, stomach and colon should be recorded, if it is less than 2 cm.
3. Number of procedures for each tumor. Current and treatment time for each procedure.
4. Type of generator and electrode.

18.2 Stereotactic body radiation therapy

SBRT implies the use of a high precision, stereotactic radiation technique. Repiratory motion of liver tumors is a challenge for obtaining this high precision. In this study it is requested that participating centers apply a technique that allows treatment of most patients with a CTV-to-PTV margin in cran-caud direction of 10 mm or smaller, and margins of 5 mm or smaller in the axial directions. Examples of approaches that may contribute to the high precision are use of a stereotactic body frame (SBF) with abdominal compression, daily imaging (in or outside the treatment room), EPID-imaging in the treatment room, use of a multi-slice CT scanner (4DCT) instead of a single slice scanner to avoid imaging artifacts, use of implanted gold markers, active breathing control (ABC), and tumor tracking (robotic Cyberknife).

18.2.1 Volume definitions

Gross target volume (GTV) The GTV is defined as the hypodense volume and the peripheral enhancing rim or what could possibly be interpreted as tumor on a contrast enhanced CT-scan. Intravenous contrast enhancement should be used with injection of 125 ml Visipaque-275 or equivalent with a flow rate of 4 ml/sec and a delay of 70 sec. (venous phase). MRI and PET to support delineation are optional. In regions with poor visibility of tumor edges, generous GTV delineation is required to avoid tumor miss.

Clinical target volume (CTV) In this study, CTV=GTV, i.e. no explicit margin is added for microscopic disease.

Planning target volume (PTV) The PTV is obtained by extending the CTV with a margin. The applied CTV-to-PTV margin should ensure that despite geometrical uncertainties (i.e. imaging artifacts in the (planning) CT-scan due to respiratory tumor motion, inter-fraction motion of the tumor, uncertainty in the set-up, residual respiratory motion during treatment, etc.) the full CTV is with a very high probability irradiated with an adequate dose. In this study, reduction of required CTV-to-PTV margins to spare critical organs in the vicinity of the tumor is not allowed.

The required CTV-to-PTV margin is dependent on the applied stereotactic approach. Prior to inclusion of patients, a participating centre has to submit a document to the QA-center, describing the technical details of the treatments, see section Credentialing. The document will be reviewed by the QA-group to approve the consistency of the margin recipy with the stereotactic approach.

18.2.2 Organs at risk (OAR)

OARs that have to be fully delineated in 3D are

- the liver
- both kidneys.

Other OARs must be delineated in the high dose volume (expected to receive more than a total dose of 5 Gy) are

- the spinal cord
- the stomach, the esophagus, bowel and the duodenum
- the heart

18.2.3 Number and size of metastases

A maximum of 4 tumors each with a maximum diameter no more than 4 cm can be treated. If additional intrahepatic tumors are found on the dose planning CT-scan, they may be treated as well and the patient will remain eligible for analysis. However, if the total number of metastases on the treatment planning CT-scan exceeds 4, the patient should be withdrawn from the study and can be treated according to local policy.

18.2.4 Planning and dose prescription

A treatment plan has to be designed with the 67% isodose tightly enclosing the PTV surface, i.e. for all points on a PTV surface the dose has to be as close as possible to 67%, but never lower. Each PTV will receive three equal fractions with one of the following four fraction dose levels:

	Prescribed PTV dose (to the 67% isodose)	**Resulting maximum tumor dose (100%)**
Dose level A	12.50 Gy	18.75 Gy
Dose level B	13.75 Gy	20.63 Gy
Dose level C	15.00 Gy	22.50 Gy
Dose level D	16.75 Gy	25.00 Gy

The dose to the PTV(s) should be the highest possible of the above mentioned dose levels (A-D), while strictly adhering to the hard OAR constraints mentioned below. If for dose level D (12.5 Gy) there are still constraint violations, the patient will be considered ineligible for treatment, but they will be included into the analysis as failures based on *the intention to treat principle*. If a dose reduction is due to constraints of the liver tissue, all tumors in one patient should be treated with the

same dose level. If dose reduction is based on localization of a tumor close to a critical normal tissue (esophagus, stomach, duodenum, bowel and kidney), it is allowed to chose a low dose level for the critical target and higher dose level for the non-critical targets,

Structure	Hard Constraint	Recommendation
Healthy liver (liver ÷ CTV)	$D_{700\ ml} < 15$ Gy	
Spinal cord	$D_{max} < 18$ Gy	
Esophagus, stomach, duodenum, bowel	$D_{1CC} < 21$ Gy for each	
Kidneys	$D_{35\%} < 15$ Gy for total kidney volume (sum of both kidneys)	
	$D_{50\%} < 15$ Gy for the kidney receiving the highest dose[(1)]	
Heart	$D_{1CC} < 30$ Gy	
Conformity index		CI < 1.5

[(1)] For one of the kidneys this constraint may be violated in case acceptable function of the other kidney has been proven with a dynamic renal scintigraphy (renography).

In case of treatment with a linac, dose planning will normally be done with ≥ 5 coplanar or non-coplanar beams. All beams will be shaped with the help of multi-leaf collimators. IMRT may be used for improved sparing of OARs.

The overall treatment time should be maximum 8 days and there should always be a minimum of 40 hours between the fractions. However, if there is more than one isocenter and they are treated sequentially, the overall treatment time may be extended to 16 days. In such case, treatment time for each isocenter should not exceed 8 days.

18.2.5 Recording and reporting

Reported to the study center are DVHs for the individual CTVs and PTVs and the liver (the CTVs should be subtracted), the minimum PTV dose, $D_{99\%}$ for the PTV, D_{700ml} for the liver (the CTV should be subtracted), D_{max} for the spinal cord, D_{1CC} for the bowel, esophagus, duodenum and stomach, $D_{35\%}$ for the total kidney volume, $D_{50\%}$ for each individual kidney,and the heart Dmax. . Aditionally, for each patient the planning CT-data, delineated contours, beam configuration, and calculated dose distribution is sent to The Technical Quality Assurance Centre (see section protocol monitoring).

18.2.6 Supportive treatment

The patients for SBRT will receive antiemetics, analgesics and H-2 blocking agents according to the local standards. The use of such agents shall be recorded in the CRF. As a standard, the treatment will be carried out on out patient basis.

19 CHEMOTHERAPY BEFORE AND AFTER STUDY TREATMENT

Chemotherapy and biological targeted therapy before as well as after the study treatment is allowed. Systemic as well as hepatic artery infusion chemotherapy is accepted. The treatments should follow the guidelines used for treatment of metastatic CRC at each site. Some patients to be included in the

trial fulfil the inclusion criteria without any chemotherapy whereas others need a decrease is tumour size or tumour extent to be possible to be included. Both these groups of patients are eligible. An adjustment for imbalance of patients receiving chemotherapy after occurrence of metastases will be performed in the final analysis. All chemotherapy given before and after the study treatment should be reported in the CRF.
The time interval between last chemotherapy and inclusion into the study should be at least 4 weeks. Systemic antineoplastic treatment should not be started within 4 weeks after the study treatment.

20 RE-TREATMENT

Re-treatment of local as well as distant recurrences by RFA, SBRT or surgical resection (whatever possible) is accepted. Re-treatment should be recorded in the CRF.

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