HOlmium radioembolization as adjuvant treatment to Radiofrequency Ablation for Early STage Hepatocellular carcinoma (HORA EST HCC): a dose-finding study

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Establishment of treatment area dose at which 90% technical success is achieved. Technical success will be defined as * 120Gy calculated radiation absorbed dose to the target area, i.e. the hyperaemic zone surrounding the area of post-RFA...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50687

Source
ToetsingOnline

Brief title
HORA EST HCC

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma, Liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Subsidie verkregen van Health Holland en Maag Lever Darm Stichting via ZonMW PTO call,Covidien Medical,Quirem Medical

Intervention

Keyword: Hepatocellular carcinoma, Holmium, Radioembolisation, Radiofrequency Ablation

Outcome measures

Primary outcome

Establishment of treatment area dose at which 90% technical success is

achieved. Technical success will be defined as * 120Gy calculated radiation

absorbed dose to the target area, i.e. the hyperaemic zone surrounding the area

of post-RFA coagulation necrosis.

Secondary outcome

* Toxicity of RFA with adjuvant segmental radioembolization as assessed by

complications according to CTCAE v4.0

* Local tumor recurrence at 6 months as assessed by multiphase CT or dynamic MRI

* Local tumor recurrence rate at 12 months as assessed by multiphase CT or

dynamic MRI

* Time-to-progression

* Progression free-survival and overall survival at 1 year

* Quality of Life

Study description

Background summary

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death in the world. Surgical resection is the first line treatment for patients with solitary HCC and a well-preserved liver function. Unfortunately, many patients with HCC are not surgical candidates due to tumor location, comorbidity or underlying liver disease, i.e. cirrhosis with portal hypertension. Radiofrequency ablation (RFA) is an effective alternative for surgical resection. Yet, local tumor recurrence rates in HCC * 2cm are higher than after surgical resection. Local tumor recurrence most frequently occurs as a result of incomplete tumor necrosis or growth of pre-existent satellite nodules. Most tumor recurrences occur in the hyperaemic zone surrounding the area of coagulation necrosis. Radioembolization is a type of brachytherapy and an effective treatment for intermediate or advanced stage HCC. Using a transarterial approach small microspheres loaded with Holmium-166 are infused into the hepatic artery. By super-selective infusion of microspheres radiation can be delivered to a segment with low toxicity to the non-tumorous liver parenchyma. It is generally recommended to deliver a dose of * 120Gy to the target area. Our study aims to establish the treatment area dose that will result in delivery of a radiation dose of * 120Gy to the target area.

Study objective

Establishment of treatment area dose at which 90% technical success is achieved. Technical success will be defined as * 120Gy calculated radiation absorbed dose to the target area, i.e. the hyperaemic zone surrounding the area of post-RFA coagulation necrosis.

Study design

In this multi-center, dose-finding study, patients with early stage hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) staging system will be included to receive percutaneous radiofrequency ablation in combination with RFA with adjuvant segmental radioembolization.

Intervention

Radiofrequency ablation
Patients will be admitted to the hospital one day before the procedure or on the day of the procedure. The procedure will be performed under general anesthesia or deep sedation. Ultrasonography and/ or CT will be used to target the tumor with a single 3cm Cooltip electrode or a 3 or 4 cm exposed tip multi-electrode Cooltip RFA probe with switch-control system (Covidien, Gosport Hamspire, United Kingdom). Ablation will be performed for 12 minutes (single electrode) or 16 minutes (multi-electrode) using standard impedance controlled ablation. Upon removal of the RFA probe the needle tract will be ablated to reduce the chance of post-procedural hemorrhage or tumor seeding. Contrast enhanced computed tomography (CECT) will be performed immediately after

ablation to confirm adequate tumor ablation. If CECT shows residual tumor enhancement, re-ablation will immediately be performed. Peri-procedural care will be in accordance with the protocol of the institution.

Radioembolization
Radioembolization consists of two sessions: pre-treatment planning and the actual treatment.
Part 1. Pre-treatment planning
Part 1 will be performed 1 day after RFA and in the same hospital admission. The first part of the radioembolization consists of an angiographic study and *test-injection* of 99m-technitium labelled macro-aggregated albumin (99mTc-MAA). The angiographic study is performed using a common femoral artery approach. Angiographic images of the celiac trunc and hepatic arteries are obtained. The vascular liver anatomy is meticulously skeletonized to identify hepatico-enteric anastomoses. If present, coil-embolization of such anastomoses will be performed if deemed necessary to enable safe radioembolization. If the planned location of infusion is distal and distant to hepatico-enteric anastomoses, these anastomoses do not need to be coiled. Coil-embolization is likely to be unnecessary in the majority of patients in the study as the injection will be super-selective, i.e. distal to the gastroduodenal artery (GDA) and right gastric artery (RGA). Using a 2.4F/ 2.7F microcatheter the segmental artery is catheterized and angiography and cone-beam computed tomography (CBCT) are performed. The CBCT will be used to verify that the segmental artery supplies the entire hyperaemic marginal zone surrounding the area of coagulation necrosis. If there is only partial opacification of the marginal zone, a second segmental artery may need to be catheterized. 99mTc-MAA is then injected into the segmental hepatic artery/ arteries feeding the tumor. Alternatively, the injection may be performed from a more proximal position, if the tumor is located at the border of two different segments. After the angiographic study with injection of 99mTc-MAA, planar scintigraphy and SPECT/CT are performed to visualize the distribution of the 99mTc-MAA. Also, SPECT imaging is performed using the handheld declipse®SPECT gamma probe. In patients with arterio-hepatovenous tumor shunting a portion of the 99mTc-MAA will bypass the hepatic capillary bed and accumulate in the lungs. If shunting to the lungs is more than 20%, there is a risk of radiation pneumonitis. Patients with a lung shunt exceeding these limits will be excluded from treatment with 166Ho. The activity of 99mTc-MAA itself is too low to cause radiation pneumonitis.

Part 2. Radioembolisation with 166Ho
Part 2 consists of the actual treatment and will be performed within 5-10 days after part 1, providing that the lung shunt is less than 20%. On the morning of the procedure baseline non-contrast enhanced MRI will be performed. Using a common femoral artery approach, angiographic images of the hepatic arteries are obtained. A 2.4/2.7F microcatheter is placed in the exact same position as where 99mTc-MAA was administered. 166Ho microspheres (QuiremSpheres®; Quirem Medical) will be used for the treatment. The required activity is calculated

according to the partition model. The volume of liver segment to be treated is calculated by measurements using cone-beam CT and/or the pre-procedural CT or MRI. The activity is chosen to deliver the desired radiation dose to the treatment zone (see 5.3). With the microcatheter in place, the catheter is connected to the microspheres delivery set. The microspheres are then delivered using a slow injection. The injection is interrupted at the discretion of the radiologist to check whether blood flow remains unobstructed by injecting a contrast medium through the microcatheter under fluoroscopic imaging. If arterial spasm occurs, boluses of 100-200 micrograms nitroglycerine may be administrated intra-arterially at the discretion of the interventional radiologist. The end-point of treatment will be the delivery of the calculated dose. If vascular stasis occurs before the entire dose has been delivered, the procedure may be ended before all microspheres have been delivered.
If no complications occur, patients will be discharged from the hospital on the day following radioembolization. No antibiotics are required. Patients are fasted at least three hours before the procedure and should have a well running peripheral venous access. Peri-procedural care and pain management will be in accordance with the protocol of the institution.

Study burden and risks

Surgical treatment is the treatment of choice for patients with early stage HCC according to the BCLC staging system. Unfortunately, many patients are not surgical candidates either due to tumor location, co-morbidity or cirrhosis with portal hypertension. The EASL recommends RFA as an alternative to resection in patients with limited disease (single tumor < 5cm or * 3 lesions of * 3cm each) and a Child Pugh A or B status. Local tumor progression rates after RFA tend to be higher than after resection, especially in tumors larger than 2 cm. Study patients are ineligible for surgical resection and will have tumors > 2cm. They are thus at an increased risk of local tumor progression. Adjuvant treatment with transarterial segmental radioembolization may potentially result in lower local tumor progression rates and thus may improve long-term prognosis.
Study patients will be subjected to a pre-procedural angiography and *test-injection* of 99mTc-MAA as well as transarterial segmental radioembolization. Percutaneous transarterial angiography and radioembolization both carry the risk of mild complications like haematoma of the inguinal region or an aneurysma spurium as a result of the femoral artery puncture. With the use of a vascular closure device, the risk of puncture site complications is approximately 1%. In rare cases a dissection of the femoral or iliac artery can occur. Although according to literature the chance is less than 2%, there is also a risk of a dissection or thrombosis of the hepatic artery.
During the pre-procedural angiography, coil-embolization of hepatic-enteric anastomosis may be deemed necessary to avoid inadvertent flow of 166Ho microspheres to the stomach or duodenum. The chance of dislocation of coils during the procedure is about 2%. In most of these cases a dislocated coil can be removed without further problems. Rarely, a dislocated coil can cause

reduction of flow in the hepatic artery, which impedes the procedure.
Radioembolization is generally well tolerated and most complications are mild. In a large European multicentre analysis of 325 patients, common procedure-related adverse events were grade 1/2 according to CTCAE v 3.0 and included nausea/vomiting (32.0% all grades) and abdominal pain (27.1% all grades), with very few grade 3 events. Fatigue was reported in 54.5% of patients (all grades), typically occurring in the first few weeks after radioembolization and lasting 1-2 weeks, with few (2.5%) grade 3 events. The percentage of patients experiencing such complications is expected to be much lower in our study. In multcenter study mentioned above, 92.6% of patient received either whole liver or lobar radiation with a median administrated activity of 1.6 GBq. In our study, treatment will be limited to one or two liver segments and the administrated activity is therefore also expected to be lower.
Events related to radiation of non-target tissues include gastrointestinal ulcerations and liver-related events. In the European multicentre study, gastrointestinal ulceration occurred in 3.7% of patients with a related mortality of 0.3%. Radiation-induced liver toxicity grade 3 occurred in 5.8% of patients. Gastro-intestinal ulceration and radiation-induced liver disease are associated with whole liver treatment and infusion of microspheres from a proximal location. These complications are therefore expected to occur less frequently in our study, as a segmental approach will be used in all patients. In a study of 84 patients treated with ultra-high dose segmental radioembolization, none of the patients developed gastro-intestinal ulcers or radiation-induced liver disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Informed consent
* Age > 18 years
* Single HCC lesion with diameter of * 2-5cm or up to three lesions with each lesion measuring no more than 3cm (confined to one liver lobe)
* HCC diagnosis is based on histology or non-invasive imaging criteria according to EORTC-EASL guidelines
* Child Pugh A or B * 7
* ECOG performance status * 2
* Bilirubin < 2mg/dL
* ASAT < 5x upper limit of normal
* ALAT < 5x upper limit of normal
* Thrombocytes * 50 X 10^9/L

Exclusion criteria

* Tumor location precluding percutaneous RFA
* Treatment area >50% of total liver volume, based on CBCT images
* Vascular tumor invasion or extrahepatic metastasis
* Main portal vein thrombosis
* Hemihepatectomy
* Severe comorbidity (e.g. cardiovascular disease, diabetes with nephropathy, active infections)
* Uncorrectable coagulopathy
* Large arterio-portovenous shunt
* Previous radiotherapy to the liver
* Surgical hepatico-enterostomy
* Hepatic resection with placement of surgical clips that may cause artefacts

on MRI
* Incompetent / mentally disabled
* Pregnancy, inadequate anticonception
* Calculated lung dose >30Gy
* Creatinine clearance < 30 ml/min

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-07-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Quirem Spheres
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO

Date:	18-01-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	12-03-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	15-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	ClinicalTrials.gov
CCMO	NL61926.058.17

Study results

Date completed:	15-03-2021
Actual enrolment:	20