Perivascular and peribiliary colorectal liver metastases (0-5 cm): irreversible electroporation versus stereotactic body radiotherapy.

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

Summary

ID

NL-OMON56964

Source
ToetsingOnline

Brief title
COLDFIRE-III

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
Colorectal liver metastases. Metastases in the liver of colon or rectal cancer.

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Angiodynamics,Gedeeltelijke funding vanuit Angiodynamics;Inc.

Intervention

Keyword: Colorectal liver metastases, Irreversible electroporation, Stereotactic body radiotherapy

Outcome measures

Primary outcome

Primary endpoint is local control at 2 years from randomization (per patient

analysis).

Secondary outcome

Secondary endpoints are local tumor progression free survival, OS, distant

progression-free survival (DPFS), time to progression (TTP), procedural

morbidity/toxicity and mortality, assessment of pain and quality of life (QoL)

and cost-effectiveness ratio (ICER).

Study description

Background summary

Colorectal carcinoma is one of the most common malignancies in the Western world, where 40-60% of the patients develop liver metastases in the course of the disease. Surgical resection is still the treatment of choice, but unfortunately up to 70% of the patients are not eligible for resection. Selected patients are offered other local treatment modalities like radiofrequency ablation (RFA) and microwave ablation (MWA). The suitability of these modalities can be limited for perivascular and peribiliary colorectal liver metastases (CRLM), when used in close vicinity to these tubular structures. The heat can damage the bile ducts and vessels, leading to biliary and vascular complications. Also, when used in the vicinity of large vessels it can lead to inadequate tumor destruction due to a *heat-sink* effect (where

blood flow in adjacent large vessels carries away the heat, thereby causing an inadequate temperature rise, leaving vital tumor cells in situ), which causes a higher percentage of local recurrences. Similarly, thermal ablation is contra-indicated for unresectable CRLM in close vicinity to other thermally sensitive structures such as the bowel (e.g. due to adhesions). Therefore, the search for new local treatment therapies is ongoing.

Irreversible electroporation (IRE) is an ablation technique that takes advantage of the electric potential gradient that exists across cell membranes. The application of a pulsating electric field across the cells alters the transmembrane potential. By reaching a sufficiently high voltage, the phospholipid bilayer structure of the cell membranes is permanently permeabilized, causing intracellular homeostasis to be disrupted, and inducing apoptosis. Recent findings resulting from animal studies using IRE on healthy (liver) tissue show a sharply demarcated treatment area, with preservation of the - acellular - connective tissue architecture and major blood vessels in the ablated area. This contrasts with thermal ablation techniques, where denaturation of proteins causes disruption of the connective tissue, destroying the anatomical framework. Electroporation leaves supporting tissue largely unaffected so the structural integrity of the walls of large blood vessels and bile ducts and bowel wall is preserved. IRE relies on electrical energy, not thermal energy, for achievement of cell death and appears to be unaffected by heat-sink. This suggests a potentially more effective treatment of an area with tumor cells near large vessels, such as centrally located liver lesions.

With these distinctive characteristics, IRE has the potential to become a successful ablation method for solid tumors in areas around large blood vessels and bile ducts, such as centrally located colorectal liver metastases (CRLM), other secondary liver tumors or early-stage hepatocellular carcinoma (HCC) that are not amenable for surgical resection or thermal ablation due to the anatomical location. Clinical trials investigating the safety of IRE in different organs have shown a safe use of this method, including the prospective VUmc pilot-study of IRE in the liver (COLDFIRE-I) and phase II trial (COLDFIRE-II).

Stereotactic body radiotherapy (SBRT) is gaining interest as another potential ablative technique to treat CRLM. Especially for solitary or a limited number of CRLM the potential to induce long-term local tumor control has been established with acceptable toxicity. Major complications that involve damage to blood vessels and bile ducts seem to occur only infrequently. Furthermore, the effectiveness of SBRT is, in contrast to RFA or MWA, not impaired by the blood flow in the vessels or the bile accumulated in the gallbladder. However, solely looking at primary local control rates following an ablative procedure seems unjust when comparing an easily repeatable technique with a one-shot treatment method (SBRT).

As the gold standard for perivascular and peribiliary CRLM (0-5 cm) is

currently undetermined, we have designed a two-arm phase-IIb/III randomized trial comparing IRE to SBRT for perivascular and peribiliary CRLM (0-5 cm).

Study objective

The primary objective of this study is to compare efficacy of IRE to the efficacy of SBRT regarding the primary endpoint (local control at 2 years) in patients with perivascular and peribiliary CRLM (0-5 cm). The CRLM are unsuitable for surgery and thermal ablation due to either comorbidities, a history of extensive abdominal surgery, a poor performance status or due to an unfavorable perivascular of peribiliary location of the tumor.

Study design

COLDFIRE III is a prospective single-center phase-IIb/III randomized trial. The primary conducting center will be the Amsterdam UMC, location VUmc.

Intervention

Patients will be randomized into one of two arms, arm A (IRE) and arm B (SBRT). The expert panel, consisting of at least two interventional radiologists, two radiation oncologists and two hepatobiliary surgeons, will appoint lesions that are ineligible for surgery of thermal ablation, and suitable for both IRE and SBRT, as target lesions.

Study burden and risks

Over the last decades, technical developments in SBRT have allowed a more precise delivery of high radiation doses per treatment fraction to the tumor. Furthermore, in some hospitals it is possible to visualize the tumor during radiation treatment to deliver gated treatment (beam-on only when the tumor is in the predetermined position) using small uncertainty margins and thereby limiting the dose delivered to surrounding healthy tissue, likely resulting in decreased toxicity. Disadvantages include the need to be positioned within a MRI bore during radiation delivery, and a prolonged time per treatment fraction. Local tumor control of SBRT for liver malignancies ranges between 50-95% after one year. A recent systematic review showed a one-year local control rate of 67% and a two-year local control rate of 59.3%; however, this systematic review also included older studies and in the last few years SBRT techniques have substantially improved. Grade I-II toxicity occurred in 23-78% of patients receiving SBRT, grade III toxicity or higher only occurred in 0-10% of patients.
IRE is a non-thermal ablation modality based on delivering pulsed electrical fields, created between needle electrodes placed in and around the tumor, that alter the existing cellular transmembrane which eventually results in cell death. IRE has the potential to become a successful alternative ablation method

for solid tumors, especially in areas around large blood vessels and vulnerable structures, such as centrally located CRLM. Prospective trials using IRE for malignancies in the liver show 1-year local tumor control of 74%, and a 1-year local recurrence free survival of 59,5%. Preclinical as well as clinical studies show a low complication profile in comparison to other local treatment modalities in these specific locations in the liver, with an overall complication rate of 40%. Because of the high voltage used with IRE, the procedure carries a small risk of inducing cardiac arrhythmias, although with the Accusync ECG gating device, which enables synchronized pulsing, no clinically significant arrhythmias have been observed within the registry. Because of the primarily non-thermal treatment effect IRE causes little damage to adjacent or inlaying vital structures. The NanoKnife IRE system is CE marked and FDA approved for image-guided ablation of soft tissue in humans.
By participating in the study, patients agree to undergo either IRE or SBRT. For each participant, the method of treatment will be decided upon by randomization. Pre-treatment screening will not be different from the standard screening for these techniques and will not be an extra burden. Both IRE and SBRT are considered safe and established treatment options for the target population.

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

- 1-3 CRLM F-18-FDG PET avid and visible on ceCT, size <=5 cm and not eligible for resection or thermal ablation due to location close to a vessel or bile duct
- No or limited extrahepatic disease (1 extrahepatic lesion is allowed, with some exclusions mentioned in the exclusion criteria)

Exclusion criteria

• Radical treatment unfeasible or unsafe (e.g. insufficient FLR);
• >10 CRLM;
• Positive para-aortal lymph nodes, celiac lymph nodes, adrenal metastases, pleural carcinomatosis or peritoneal carcinomatosis;

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2024
Enrollment:	96
Type:	Anticipated

Ethics review

Approved WMO Date:	20-08-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
CCMO	NL83557.018.23