COLLISION trial - Colorectal liver metastases: surgery versus thermal ablation - a phase III prospective randomized controlled trial

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON54713

Source
ToetsingOnline

Brief title
COLLISION - Surgery versus ablation for colorectal liver metastases

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Metastases
- Hepatobiliary therapeutic procedures

Synonym
Colorectal cancer liver metastases; Metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: KWF ¤ 382.979;97 en/of ZonMw ¤ 480.201;07,Medtronic B.V.,Medtronic-Covidien voor ¤ 580.000

Intervention

Keyword: Colorectal cancer, Colorectal liver metastasis, Microwave ablation, Radiofrequency ablation

Outcome measures

Primary outcome

Primary endpoint is OS (intention-to-treat analysis).

Secondary outcome

Main secondary endpoints are overall disease-free survival (DFS), time to progression (TTP), time to local progression (TTLP), primary and assisted technique efficacy (PTE, ATE), procedural morbidity and mortality, length of hospital stay, assessment of pain and quality of life (QoL), cost-effectiveness ratio (ICER) and quality-adjusted life years (QALY).

Study description

Background summary

Colorectal carcinoma is one of the most common malignancies in the Western world. In the course of the disease 40-60% of patients develop colorectal liver metastases (CRLM). Without treatment survival for these patients is cumbersome with a median overall survival (OS) of 7.4 - 11 months. Surgical resection represents the historical standard and treatment of first choice with 5-year OS reaching 35-60%. To eliminate unresectable metastases, several ablative strategies have emerged. Thermal ablation techniques employing radiofrequency ablation (RFA) and microwave ablation (MWA) have slowly worked their way into common clinical practice and international guidelines. Thermal ablation for small liver lesions has an excellent safety profile with a low complication rate for smaller liver tumors. However, the issue of local site recurrence

after thermal ablation has prohibited widespread adoption of the technique for resectable lesions. In the last few years, thermal ablation techniques have substantially improved with primary efficacy rates (complete ablation after the first procedure) for lesions <=3cm now reaching 92-100%. These results are comparable to recurrences after surgical resection for similar-sized lesions. The relative ease to percutaneously re-ablate potential site recurrences, nowadays often in the setting of a one-day admission under conscious sedation, has downgraded the relevance of LSR with local control rates (assisted technique effectiveness) approaching 100% for lesions <=3cm. The recently presented long-term results from the EORTC CLOCC-trial (ASCO 2015) show a clear survival benefit of RFA plus systemic chemotherapy over chemotherapy alone for unresectable CRLM: 8-year OS 36% vs 8.9% (p=0.01; HR 0.58; 95%CI 0.38-0.88). Numerous studies have demonstrated a superior safety profile in addition to lower direct and indirect costs of thermal ablation over surgical resection. Despite this, the 5-year OS (range 15-62%) of thermal ablation for patients with unresectable CRLM has been labelled inferior to surgical resection for patients with resectable CRLM according to previous meta-analyses and systematic reviews. Because the groups are by definition confounded by indication these results should be interpreted with care. The apparent selection bias, when comparing patients with unresectable disease to surgical candidates, the superior safety profile, and the competitive overall survival results for the more recent reports, mandate the setup of a randomized controlled trial. We have designed a two-arm phase-III randomized controlled trial comparing surgical resection (standard of care) to thermal ablation (experimental arm) for resectable and ablatable CRLM <=3cm.

Study objective

The primary objective is to prove non-inferiority of thermal ablation compared to hepatic resection in patients with at least one resectable and ablatable CRLM (<=3cm) and no extrahepatic disease.

Study design

COLLISION is a prospective multi-center phase-III randomized controlled trial. We hypothesize that thermal ablation is non-inferior to surgery for the selected patient groups in terms of the primary objective (overall survival). The Cox proportional hazards model (1-sided; non-inferiority or superiority) is used for sample size calculations. Given the superior safety profile we consider a hazard ratio of 1.3 to represent the upper limit of non-inferiority (non-inferiority margin). An HR of 1.3 corresponds to a 56.5% chance of the ablated patients to die first ((P = HR/(1 + HR) = 1.3/(1 + 1.3) = 0.565 (56.5%)). With 3 years of patient accrual and five years of follow-up we will have reached 60% of events (death) in approximately 6.5 years (overall probability of event, pE =0.6). The calculated sample size therefore is 599 (NS).To account for a 10% drop-out ratio (NDO=69) prior to randomization and a

3% loss to follow-up (NLTFU=18) after randomization we need to include 687 patients (NI). A total number of 618 patients will be randomized (NR) into one of two arms: arm A will undergo surgical resection (n=309) and arm B thermal ablation (n=309) for appointed target lesions.

Intervention

Eligible patients will be stratified into low-, intermediate- and high disease burden after assessment by an expert panel. The panel, consisting of at least two diagnostic radiologists, two interventional radiologists and two hepatobiliary and/or oncological surgeons, will appoint lesions that are resectable and ablatable as target lesions, resectable and unablatable lesions as unablatable lesions and ablatable but unresectable lesions as unresectable lesions. All unablatable lesions should be resectable and all unresectable lesions should be <=3cm and ablatable.

Low disease burden: 1-3 CRLM <=3cm, no unablatable or unresectable lesion(s).
Intermediate disease burden: >=1 target lesion(s), and >=1 unablatable lesion(s) requiring minor surgery or unresectable lesion(s) requiring ablation(s).
High disease burden: >=1 target lesion(s), and >=1 unablatable lesion(s) requiring major surgery (trisegmentectomy, (extended) hemihepatectomy).

Eligibility needs to be reconfirmed during the surgical procedure. Hereafter patients will be randomized to undergo surgical resection of the target lesions (allowing thermal ablation for additional unresectable lesions) or thermal ablation (allowing resection for additional unablatable lesions).
Postprocedural care will be identical between the two groups with the exemption that hepatic recurrences (either local site recurrence or new lesions) suitable for both resection and ablation will again be treated with the technique used to treat the initial target lesion(s). Conferring to national guidelines follow-up will include imaging, laboratory tests including tumor markers (CEA) and quality of life questionnaires. Since every local center uses different imaging techniques, the method of imaging is chosen by local expertise.
Patients with recurrences that are considered unsuitable for additional focal therapy will be re-referred to their medical oncologist to assess additional systemic chemotherapy. In the event of chemotherapeutic down-staging hereafter, focal therapy can be reconsidered.

Study burden and risks

Reported outcomes after thermal ablation for CRLM are improving. Survival results after thermal ablation for non-surgical candidates have approached the results achievable with surgery for resectable disease. The superior safety profile and the suggested lower overall costs of thermal ablation over surgical resection, stress the need to conduct a randomized controlled trial for patients with small resectable and ablatable CRLM. By participating in the

study, patients agree to either undergo standard treatment for hepatic metastases by means of hepatic resection, or to undergo the method studied which is open thermal ablation of the metastases. For each participant, the method of treatment will be decided upon by randomization. Pre-operative screening will not be different from the standard treatment and will not be an extra burden. If participants will receive treatment with thermal ablation, we anticipate less peri-operative complications and hence a shorter hospital stay. Follow-up after the procedure will be identical to standard treatment. If our hypothesis will prove to be wrong, patients having undergone thermal ablation are at risk of having a shorter overall survival, shorter disease-free survival, and higher local recurrence rate, leading to a lower quality of life. If thermal ablation proves to be indeed non-inferior to surgical resection in this patient group, patients having undergone ablation will have had a less invasive procedure with presumably shorter hospital stay and fewer postoperative complications, with comparable overall survival. In a broader sense, if our hypothesis will prove right, a switch in treatment-method for the group studied will lead to a lowering in overall post-procedural morbidity and mortality and length of hospital stay. Moreover, this will likely lead to improved quality of life. Subsequently, a cost-benefit analysis may prove beneficial for treatment with thermal ablation with respect to overall hospital and treatment costs given the well-known direct and indirect costs of both procedures.

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

• Histological documentation of primary colorectal tumor;
• At least one CRLM size <= 3 cm eligible for both surgical resection and thermal ablation (target lesions);
• Additional unresectable CRLM should be <= 3 cm and ablatable (unresectable lesions);
• Additional unablatable CRLM should be resectable (unablatable lesions);
• Maximum number of CRLM 10;
• Resection for resectable lesions considered possible obtaining negative resection margins (R0) and preserving adequate liver reserve
• Resectability and ablatability should be re-confirmed intra-operatively by US plus full exploration for hepatic, peritoneal and regional lymph node metastases;
• Age >18 years;
• Eastern Cooper ative Oncology Group performance status (ECOG) 0-2;
• American Society of Anesthesiologists (ASA) grade 1-3;
• Life expectancy of at least 12 weeks;
• Written informed consent

Exclusion criteria

• Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment;
• Immunotherapy <= 6 weeks prior to the procedure;
• Chemotherapy <= 6 weeks prior to the procedure;
• Any surgical resection or focal ablative liver therapy for CRLM prior to inclusion;
• Severe allergy to contrast media not controlled with premedication;
• Patients with only one or two small-size (0-3cm) and anatomically deep-seated (defined as requiring major hepatectomy) CRLM in a single liver

lobe

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-08-2017
Enrollment:	637
Type:	Actual

Medical products/devices used

Generic name:	Radiofrequency ablation (RFA) and microwave ablation (MWA)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	29-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-08-2023

Application type:	Amendment
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	NL58551.029.16