Project Proposal

COLLISION-XL trial:

UNRESECTABLE COLORECTAL LIVER METASTASES:

STEREOTACTIC BODY RADIOTHERAPY VERSUS MICROWAVE ABLATION

a phase II prospective randomized controlled trial for CRLM 3 - 5 cm

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PROTOCOL TITLE

'COLLISION XL trial – UNRESECTABLE COLORECTAL LIVER METASTASES: STEREOTACTIC BODY RADIOTHERAPY VS MICROWAVE ABLATION a phase II prospective randomized controlled trial for intermediate-size (3 – 5 cm) colorectal liver metastases

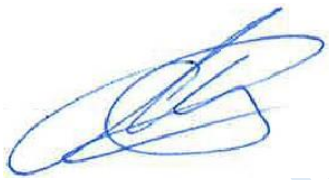
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Principal investigators: **Amsterdam, AUMC**	MR Meijerink, MD, PhD Department of Interventional Oncology Amsterdam University Medical Centres (AUMC) De Boelelaan 1117 1081 HV Amsterdam, the Netherlands P. Van Rossum, MD, PhD Department of Radiation Oncology Amsterdam UMC (AUMC), Amsterdam De Boelelaan 1117 1081 HV Amsterdam, the Netherlands
Local principal investigators **Ede, ZGV**	C Sietses, MD, PhD Department of Surgery

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Groningen, UMCG	AL Diederik, MD Department of Interventional Radiology S.J.S. Ruijter, PhD Department of Surgery
Project coordinators	S. van der Lei, MD, PhD Candidate Department of Interventional Radiology Amsterdam UMC, Amsterdam
Co-investigators:	A Bruynzeel, MD, PhD, Amsterdam UMC (AUMC) B Slotman, MD, PhD, Amsterdam UMC (AUMC) JJJ de Vries, MD, Amsterdam UMC (AUMC) BB van der Meijs, MD, Amsterdam UMC (AUMC) MP van den Tol, MD, PhD, Amsterdam UMC (AUMC) B Zonderhuis, MD, Amsterdam UMC (AUMC) G Kazemier, MD, PhD, Amsterdam UMC (AUMC)
Epidemiologists	Birgit I. Lissenberg-Witte
Financial controller	Sergio Verhaeg
Sponsor (in Dutch: verrichter/opdrachtgever)	Amsterdam UMC (AUMC), location VUmc
Independent expert (s)	S Ramsoekh, MD, PhD, Amsterdam UMC (AUMC)
Laboratory sites	VU University Medical Centre, Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands

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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head Department of Radiology C van Kuijk, MD, PhD VU University Medical Centre De Boelelaan 1117 1081 HV Amsterdam		15-01-2019
Coordinating Investigator/Project: MR Meijerink, MD, PhD Department of Radiology & Nuclear Medicine VU University Medical Centre De Boelelaan 1117 1081 HV Amsterdam		15-01-2019

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AJCC	**American Joint Committee on Cancer**
AE	**Adverse Event**
CA	**Competent Authority**
CEA	**Colon Early Antigen**
Ce	**Contrast enhanced**
CRB	**Clinical Research Bureau**
CTV	**Clinical target volume**
CRLM	**Colorectal liver metastases**
DSMB	**Data Safety Monitoring Board**
EORTC	**European Organization for Research and Treatment of Cancer**
GCP	**Good Clinical Practice**
GTV	**Gross tumour volume**
HR	**Hepatic resection**
IOUS	**Intraoperative ultrasound**
LOS	**Length of hospital stay**
LSR	**Local site recurrence**
LTPFS	**Local tumour progression free survival**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MWA	**Microwave ablation**
AOR	**Organs at risk**
OS	**Overall survival**
PFS	**Progression-free survival**
PTV	**Planning target volume**
QLQ	**Quality of life questionnaire**
QoL	**Quality of life**
RFA	**Radiofrequency ablation**

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(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.**
SPSS	**Social sciences software**
SBRT	**Stereotactic Body Radiotherapy**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WBP	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

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SUMMARY

Rationale: 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. Although chemotherapeutic regimens are slowly improving, local therapy for CRLM remains the only option associated with a realistic chance of long-term disease control or in selected cases even full cure. Surgical resection represents the historical standard and treatment of first choice with 5-year OS reaching 35-60%. However only a minority of the patients (i.e. 10-20%) is eligible for surgery due to size, number or location of the metastases, or relevant co-morbidities. 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 tumours. 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 local site recurrence (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.

Stereotactic body radiotherapy (SBRT) is gaining interest as a potential means to treat CRLM. Especially for solitary or a limited number of CRLM the potential to induce long-term local tumour

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control has been established with acceptable toxicity. Several recent propensity matched comparisons from the radiation oncology community seem to favour SBRT over thermal ablation for lesions >3cm, substantiated by a superior local tumor progression free survival following the initial treatment.

In their response, the interventional oncology communities state that simply comparing local control rates following an ablative procedure seems unjust when comparing an easily repeatable technique with a one-shot treatment method. Furthermore, the claim that SBRT is less-invasive because it is a no-needle technique seems unsubstantiated and may well be prejudiced given the unquestionably larger area of collateral damage following SBRT.

Given the results from the EORTC-CLOCC trial, the comparable survival for ablation + surgery versus surgery alone, the potential to induce long-term disease control and the very low complication rate following percutaneous ablations for CRLM ≤ 3 cm and given the fact that the local control rate has approached 100% for smaller CRLM, we believe SBRT is currently not indicated for thermally ablatable CRLM ≤ 3 cm.

However, thermal ablation local control rates clearly descent with increasing tumour-size and the number of complications will rise. Hence, we believe clinical and oncological equipoise for CRLM 3 – 5 cm has been reached for unresectable CRLM treated with either MWA versus SBRT.

We have designed a two-arm phase-II randomized controlled trial comparing SBRT to MWA for unresectable CRLM 3 – 5 cm.

Objective: The primary objective of this study is to compare efficacy of MWA to the efficacy of SBRT with regards to the primary endpoint (local tumour progression free survival at 1 year [1-year LTPFS]) in patients with unresectable CRLM (3 – 5 cm) that are unsuitable for surgery due to either comorbidities, a history of extensive abdominal surgery, a poor performance status or due to a certain unfavourable anatomical location of the tumour.

Study design: COLLISION XL is a prospective multi-centre phase-II randomized controlled trial.

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Study population: 68 patients with 1-3 unresectable lesions of 3 - 5cm, unsuitable for (further) chemotherapy regimens, suitable for both MWA and SBRT and no or limited extrahepatic disease (1 extrahepatic lesion is allowed, not including positive para-aortal lymph nodes, celiac lymph nodes, adrenal metastases, pleural carcinomatosis or peritoneal carcinomatosis) are considered eligible. Supplementary resections for resectable lesions and thermal ablations for unresectable CRLM ≤3cm are allowed. A maximum number of 10 CRLM are allowed for patients with no extrahepatic disease and a maximum number of 5 lesions are allowed for patients with limited extrahepatic disease.

Intervention: SBRT or MWA. The panel, consisting of at least two interventional radiologists, two hepatobiliary surgeons and two radiation oncologists, will appoint lesions of 3-5cm that are unresectable and suitable for both MWA and SBRT, as target lesions. All lesions that are not suitable for ablation should be resectable and all unresectable lesions <3cm should be suitable for thermal ablation.

Main study parameters/endpoints: Primary endpoint is local tumour progression free survival (LTPFS) at 1 year from randomization. Secondary endpoints are local tumour progression free survival time, OS, disease-free survival (DFS), time to progression (TTP), procedural morbidity/toxicity and mortality, assessment of pain and quality of life (QoL) and cost-effectiveness ratio (ICER).

Quality assurance protocol: A quality assurance protocol will guarantee the welfare of trial participants, the quality of local treatment protocols as well as the integrity of data collection.

Follow-up: The follow-up period will be at least one year following randomization or until the date of death from any cause. The formal starting time of study participation will be from the date of randomization.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Over the last decades, technical developments made it possible to deliver high

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radiation doses per treatment fraction more precisely to the tumour, called stereotactic body radiotherapy (SBRT). Furthermore, in some hospitals it is possible to visualize the tumour during radiation treatment to deliver gated treatment (beam-on only when the tumour is in the predetermined position) using small uncertainty margins and thereby limiting the dose delivered to surrounding normal organs, likely resulting in decreased toxicity. Disadvantages include the need to be positioned within the MRI bore during radiation delivery, and a prolonged time per treatment fraction. Local tumour 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.

Reported outcomes after thermal ablation for CRLM are improving. Survival results after thermal ablation for non-surgical candidates for lesions <3cm have approached the results achievable with surgery for resectable disease. However for lesions >3cm the local control rate decreases significantly. In a study from Tanis et al local recurrence rate was 21.4% after RFA for lesions >3cm, this is in accordance with the findings of Mulier et al where the local recurrence rate after surgical RFA for liver tumours of 3-5cm was 21.7%. Local recurrence after MWA for liver tumours >3cm showed a similar rate of 23%. Major complications occur in 2-4% of patients receiving MWA.

By participating in the study, patients agree to undergo either SBRT or MWA. 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 SBRT and MWA are considered safe and established treatment options for the target population.

At the moment it is uncertain whether SBRT or thermal ablation is preferable for intermediate size unresectable CRLM. No randomized controlled trials comparing SBRT to MWA in CRLM have been conducted so far. If this study shows that the efficacy of one technique is superior over the other this could lead to a prolonged LTPFS for patients with CRLM, reducing the number of required repeat procedures and potentially improving disease free and overall survival.

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1. INTRODUCTION AND RATIONALE

1.1 Clinical background

Colorectal cancer is the second most common cause of cancer related death in developed countries and the third most common malignancy worldwide with approximately 1.4 million new cases every year(1). Roughly fifty percent of patients develop colorectal liver metastases (CRLM), yet only a minority (10–15 %) can undergo hepatic resection(2). Five-year overall survival (OS) following liver resection ranges between 31 % and 58 % in carefully selected patients(2, 3). Up to 40-60% of the patients with colorectal cancer will develop metastases in the course of their disease, the liver being most frequently affected. The prognosis of patients with untreated CRLM (receiving only symptomatic therapy) is poor, with OS 4.5 - 12 months, depending on extent of metastatic disease at the time of diagnosis(4). Median OS of metastatic colorectal cancer patients treated with first-, second- and, especially for patients with exon 2 wild-type KRAS, third-line combination chemotherapy has improved but remains humble at 15-20 months(5, 6).

Surgical resection of the metastases has long been considered the only curative treatment option. Despite technical improvements, still only 20-30% of the patients are found eligible for surgery, either because the tumour number or distribution will result in inadequate residual liver volume if resected or an inability to achieve margins because of tumour location adjacent to the vena cava and hepatic confluence, the presence of extrahepatic disease, or concomitant comorbidity(7-9). If all macroscopically visible tumour tissue is amenable for surgery, resection can result in a 5 year OS of 23-58%(10).

In the past decades interstitial ablative techniques have been developed as a treatment modality for patients with unresectable liver tumours such as percutaneous ethanol injection, cryo-ablation and heat-inducing methods such as laser-ablation, radiofrequency ablation (RFA) and microwave ablation (MWA). RFA and MWA are the most widely adopted ablation modalities.

In the past few years, surgical resection has been challenged by these ablative therapies(11). Current literature provides intriguing information regarding the results of RFA and MWA. Applied to unresectable CRLM, 5-year survival rates are approaching the results reported after surgical

resection, especially for patients presenting with a limited number of small-size lesions. Abundant studies have reported 5-year OS ranging 25-55%(12-251). The recently presented long-term results from the only available randomized controlled trial (CLOCC) show a survival plateau of 36% after 8-years in patients with unresectable CRLM(252). Subgroups of patients with metastases ≤2.5-4cm have a better prognosis(84, 229).

In the Dutch guidelines, SBRT should be considered a treatment option for unresectable CRLM if the location is unfavourable for thermal ablation(253). It can be administered safely even when a lesion is located in proximity to the gallbladder, bile ducts, main vessels and the diaphragm. No anaesthesia is required and recent advances in SBRT techniques seem to have reduced radiation induced toxicity. Nonetheless, major complications still occur in 0-9% and toxicity grade I-II occurs in 23-78% of patients(254-259).

The 1-year local control rate ranges between 50-95%, with some studies suggesting that size of the lesion affects local control rate(257, 258, 260). Most studies concerning SBRT are retrospective or prospective cohort studies.

1.2 Microwave ablation

Microwave ablation utilizes dielectric hysteresis to produce heat. Tissue destruction occurs when tissues are heated to lethal temperatures from an applied electromagnetic field, typically at 900–2500 MHz. Polar molecules in tissue such as H2O are forced to continuously realign with the oscillating electric field, increasing their kinetic energy and, hence, the temperature of the tissue. Tissues with a high percentage of water (as in solid organs and tumours) are most conducive to this type of heating. MWA has several theoretical advantages that may result in improved performance near blood vessels. During RFA, the zone of active tissue heating is limited to a few millimetres surrounding the active electrode, with the remainder of the ablation zone being heated via thermal conduction(261). Owing to the much broader field of power density (up to 2 cm surrounding the antenna), microwave ablation results in a larger zone of active heating. This increased zone allows for a more homogeneous zone of tumour cell death, both within the targeted zone and next to blood vessels. This feature is thought to make MWA less affected by heat sink, although our results contradict this assumption. We only included patients treated with the first generation MWA system employing 915 MHz. Recent

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developments in the field of MWA, employing higher frequency bands (2.45 GHz) or spatial energy control (thermal, field, and wavelength), claim to create more predictable, larger and more spherical ablation zones regardless of target location, tissue type or changes in tissue properties during the ablation(262).

Mortality, adverse events and quality of life

Both Shibata et al. and Tanaka et al. did not detect any mortality after MWA or surgery within 60 days after the procedure(202, 263). Three observational studies reported mortality ranging 0-2%(216, 264, 265). Shibata et al. reported complications in 2/14 patients in the MWA-group (1 liver abscess, 1 biliary fistula) and in 3/16 in the surgery group (1 intestinal obstruction, 1 biliary fistula, 1 wound infection) (p = 0,87)(202). Tanaka et al. found complications in 6/37 patients undergoing liver surgery vs 3/16 in the combined group (no p=value reported)(263). In observational studies the documentation of complications is heterogeneous with rates varying between 0-54%(216, 265-269). No studies reported the effect on quality of life.

Progression free and overall survival

Shibata et al. reported a median DFS of 13.3 months following surgery vs. 11.3 months following MWA(202). Tanaka et al. did not detect significant differences in recurrence free survival (4-year OS: 39% vs. 35%; p = 0.86)(263). After a median follow-up of 21 months 28/34 (19 in the liver) patients in the surgery group had a recurrence vs. 11/15 (9 in the liver) in the MWA group after a median follow-up of 19 months. Eng et al. reported a 3.5-year DFS of 19%(267). Stattner et al. found a 3-year OS of 22% for the entire MWA group and 32% for the MWA alone subgroup(216). Two studies found a median DFS of 8 and 12 months(216, 265). Groeschl et al. reported a 3- and 5-year DFS of 34% and 9%(270). In a second series Groeschl et al. found a 3-year DFS of 0%(268). Overall recurrence ranges between 39-72%(216, 265, 267, 268, 270). In 8 case series LSR varied between 2-30%(216, 265-271).

For lesions >3cm the local control rate decreases significantly. In a study from Tanis et al (222) local recurrence rate was 21.4% after RFA for lesions >3cm, this is in accordance with the findings of a systematic review where the local recurrence rate after RFA for liver tumours of 3-5cm was 24.5% (272). Local recurrence after MWA for CLRM>3cm showed a similar rate of 23%(273).

Engstrand et al. reported a 4-year OS of 41% for MWA vs 4% in the historical cohort treated with chemo alone(274). This effect withstood multivariate analysis (HR = 0.56; 95%CI 0.33 – 0.96). The 4-year OS in the surgery alone cohort was 70%, although no formal statistical comparison with surgery alone was reported. Shibata et al. reported a 3-year OS of 23% after hepatectomy and 14% after MWA(202). Median OS was 25 vs 27 months. These differences were non-significant. Tanaka et al. did not detect any significant differences in OS between MWA plus surgery vs. surgery alone (3-year OS: 50,9% vs. 48.8%)(263). Median OS was 39 months after surgery and 28 months after MWA plus surgery. In multivariate analysis MWA was no prognostic factor for OS. Median OS in five case series ranged between 24 and 36 months(216, 265, 268, 270, 271). The reported 3-,4- and 5-year OS varied between 35-79%, 35-58% and 17-18%(216, 264, 265, 267-271, 275).

1.3 Stereotactic body radiotherapy

Over the recent decades, radiotherapy in the treatment of liver tumours has emerged. Earlier, conventional radiation treatments could treat the whole liver safely only up to doses that led to palliation of symptoms, due to radiation induced liver disease (RILD) (276). This disease is characterized by ascites, increased weight, girth and increased levels of alkaline phosphatase (277). Technical developments made it possible to deliver high radiation doses to a specified target without concurrent damage to the surrounding healthy tissue, referred to as stereotactic body radiotherapy (SBRT) (277). Furthermore, magnetic resonance (MR)-guidance makes it possible to visualize the tumour during radiation delivery. With this technique, radiation can be delivered “gated” (i.e. beam-on only when the tumour is in the predetermined position) using small uncertainty margins and thereby limiting the dose delivered to normal organs, likely resulting in decreased toxicity (278, 279). Most hospitals currently don’t have access to MR-guided SBRT and use other techniques.

Currently, the Dutch guideline *‘Colorectal carcinoma’* states to consider the use of SBRT for the treatment of unresectable CRLMs that have an unfavourable position for RFA or MWA (280). 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 (281). Furthermore, external radiotherapy has no

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restrictions on reaching any tumour location in the liver, such as the sub-diaphragmatic region, which may be more difficult to approach with thermal ablation techniques (281).

Safety and efficacy of SBRT

A variety of studies investigating SBRT as a treatment modality for liver tumours have been published. Currently, there are no randomized phase III trials. There are mostly retrospective and prospective cohort studies on SBRT for liver tumours (257, 260, 281-292). Ten studies were prospective (257, 260, 281, 283-285, 287-289, 292) and four were retrospective (282, 286, 290, 291). Radiation doses and number of fractions varied substantially between studies. Reported complications included fatigue (260, 282, 284, 286, 287, 292), elevation of liver function tests (260, 281-283, 286, 287, 292), nausea (260, 282, 284-286, 292), vomiting (292), diarrhoea (285), pain (284, 285, 287, 288, 290, 291), gastric or duodenal inflammation, ulceration or bleeding (260, 283-285, 291), portal vein thrombosis (283) and portal hypertension syndrome (281, 288, 290). The study by Hoyer et al. (285) reported the death of one patient 7 weeks after SBRT, caused by hepatic failure. It could not be established whether this fatal incidence was caused by radiation induced hepatitis or to thrombosis. Furthermore, a study by Méndez Romero also reported the death of one patient within a month after SBRT, but this patient was treated for hepatocellular carcinoma (HCC) and also had a comprised liver function and cirrhosis beforehand (Child-Pugh grade B) (293).

One-year local control rate ranges between 50% to 95% (257, 260, 281-284, 286, 287, 290, 292), two-year local control rate between 45.0%-92% (257, 282, 284-286, 288-292). Ten studies reported overall survival (257, 260, 282, 284-288, 290, 292). Median overall survival ranged from 14.5 to 37.5 months after a median follow-up period ranging from 12 to 26 months. However, these survival rates are difficult to interpret due to heterogeneity in the included patients between studies. A variety of studies included both primary liver malignancies as well as liver metastases, and in case of metastases some studies included metastases that had various primary tumour histology.

1.4 Clinical risk score

In the past, several clinical risk scores (CRS) for the outcome of patients with CRLM have been published(294-302). In 1999, Fong et al. described the most widely used CRS(303). This prognostic scoring system has been verified by independent investigators(304). Several authors

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have proposed the concept of stratification by CRS in relation to the effects of a multimodal treatment strategy on OS. These authors suggest that patients with a high risk score have a worse prognosis and might therefore benefit more from chemotherapy compared to patients with a low risk score(305, 306).

Table 1: Fong's clinical risk score for tumour recurrence (CRS)

Points	Criterion
1	Node-positivity primary
1	<12 months disease free interval
1	>1 liver tumours
1	Largest tumour >5cm
1	CEA >200 ng/mL
Score 0-5	**at time of diagnosis liver metastases*

As described earlier, efforts to improve outcome of liver surgery by combining the resection with chemotherapy have failed to demonstrate definite OS benefit. This may partly be due to the fact that these studies involve strict protocol inclusion criteria. Consequently, patients with a high clinical risk score - which might benefit the most from chemotherapy - are often underrepresented in these studies. Since genuine survival benefit has not yet been demonstrated, could this low impact of chemotherapy on survival then be explained by the relatively low risk profile of the patients included in these trials?

The correlation between lesion-size and outcome in terms of both local failure and overall survival after thermal ablation is strong and well established(20, 22, 24, 26, 28, 61, 66, 307). Likewise, neo-adjuvant chemotherapy may downstage patients to less-invasive surgical resections and reduce peri-operative complications in selected patient groups(308, 309). Given the high objective response rate of first line oxaliplatinum based chemotherapy (> 80%), there is a rationale to give neo-adjuvant chemotherapy prior to thermal ablation and surgical resection in patients with more extensive disease and/or a higher clinical risk score (CRS >4).

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1.5 Chemotherapy

The Dutch oncology guidelines state that patients with primary unresectable, but potentially resectable CRLM, should be ablated or if this is not possible treated with at least doublet chemotherapy in combination with targeted therapy (310). The primary objective is downsizing of CRLM to make secondary resections and / or ablations possible. Hepatotoxicity of systemic treatment can increase surgical morbidity (311-314). So preferably, duration of neoadjuvant chemotherapy should not exceed 4 months of treatment whenever CRLM are resectable or ≤3cm and suitable for any other local ablative technique.

Patients with at least one CRLM >3cm considered either permanently unresectable or in whom down staging to resectable disease failed, should continue chemotherapy until disease progression or unacceptable toxicity is objectified before considering thermal ablation or SBRT. The Dutch CAIRO 5 study is a multicentre, randomised, phase 3 clinical study that will evaluate what the optimal neoadjuvant induction regimen is for colorectal cancer patients with unresectable liver-only metastases (primary endpoint is progression-free survival).

1.6 Extrahepatic disease

Several studies have shown a worse outcome for patients with hepatic and extrahepatic disease(315). Nevertheless, retrospective series have shown that long term survival can be achieved in this specific group. One meta-analysis that included 1.152 patients with simultaneous extrahepatic disease showed long term survival after radical resection of both the hepatic and the extrahepatic lesions(315). Although controversial, an increasing subset of patients are offered surgical resection, stereotactic ablative radiotherapy or thermal ablation of pulmonary metastases with similar results regarding outcome according to series using either multivariate analysis or case matching(316-323). After complete resection of extrahepatic metastatic sites 5 year survival rates of 40-68% can be achieved(84, 324, 325). Approximately 5-10% of the colorectal cancer patients will have metastases in both liver and lungs. In selected patients combined resection of lung and liver metastasis is feasible and 5 year survival rates of 30-60% have been reported(325-328). One has to realize that these reports concern a specifically selected group of patients and 5-year survival rates are therefore highly biased(319). For patients with >1 extrahepatic site or with involvement of the celiac axis lymph nodes or the adrenal gland,

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prognosis is cumbersome and focal tumour eradication seems unbeneficial over systemic chemotherapy alone. Whether maximum debulking for patients with more extensive extrahepatic metastatic colorectal carcinoma improves survival will hopefully be shown in the currently ongoing ORCHESTRA trial (primary endpoint overall survival) (329).

1.7 Study rationale

Current guidelines in the Netherlands state that thermal ablation can be applied for unresectable CRLM of limited size (up to 3cm) and that SBRT should be considered if the location of the lesion is unfavourable for thermal ablation(253). It does not clarify what treatment option is preferable for intermediate size CRLM (3-5cm). The current primary efficacy rate of thermal ablation (complete ablation after the first procedure) for CRLM ≤3cm (92-100%) is comparable to recurrences at the resection plane after surgery for similar sized lesions (193, 216, 268, 270, 330). However, multiple studies have shown that efficacy significantly decreases to below 80% when CRLM size is >3cm (222, 270, 273).The 1-year local control rate for SBRT in different studies (all retrospective or prospective cohort studies) ranges from 50-95%. In some of these studies increasing tumour size also had a negative influence on the local control rate(257, 258, 260). Both techniques have a low complication rate. SBRT could be considered as even less invasive than MWA, plus you don't have to sedate the patient for this procedure; however, late toxicity is a possible complication and it is rarely possible to perform SBRT more than once on the same CRLM. It is still unclear what the preferable treatment is for patients with unresectable intermediate size (3-5cm) CRLM with curative intent. We would like to investigate this in the setting of a randomized controlled trial.

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2. OBJECTIVES

The main objective is to compare 1-year local tumour progression free survival (LTPFS) of MWA to SBRT in patients with at least one unresectable intermediate size (3-5cm) CRLM that is suitable for both SBRT and MWA. We hypothesize that both treatment modalities will be comparable in regard to LTPFS, which is the primary endpoint. Main secondary endpoints are toxicity/adverse events, overall survival (OS), overall disease-free survival (DFS), assessment of pain and quality of life (QoL) and cost-effectiveness ratio (ICER).

2.1 Primary outcome

Primary objective is to compare 1-year local tumour progression free survival (LTPFS) in both study arms. Local tumour control rate is defined as the percentage of target tumours successfully eradicated 12 months after treatment, according to the RECIST and PERCIST criteria (331, 332). Ablation site recurrences within the first 6 months that are successfully retreated using the same technique (re-MWA or re-SBRT) do not qualify as local recurrence.

2.2 Secondary outcomes

To compare the following parameters for the two treatment arms:

- Local tumour progression free survival time (LTPFS; *per lesion analysis*);
- Overall survival (OS; *per patient analysis*): OS is defined as the time from focal therapy to the time of death due to any cause;
- Disease free survival (DFS; *per patient analysis*): DFS is defined as the time from focal therapy to the time of local disease progression, new metastases or death (events);
- Time to progression (TTP; *per patient analysis*): TTP is defined as the time from focal therapy to the time of local disease progression, new metastases (events) censoring the date of death from any cause (censor);
- Distant progression free survival (DPFS; *per patient analysis*): DPFS is defined as the time from focal therapy to the time of distant disease progression or death (events);
- Rate of adverse events and serious adverse events (AE and SAE; *per procedure analysis*), associated with both treatment arms;

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- Pain assessment using visual analogue scale questionnaires (VAS; *per procedure analysis*: Assessed prior to, directly after and every three months after local treatment;
- Quality of life assessment using EORCT QLQ-C30, EQ-5D, and PRODISQ questionnaires (*per procedure analysis)*: Assessed prior to, and two weeks, three months and six months after local treatment;
- Direct and indirect total costs of care per treatment arm; quality-adjusted life years (QALY) and incremental cost-effectiveness ratio (ICER) per treatment arm (*per patient analysis*);

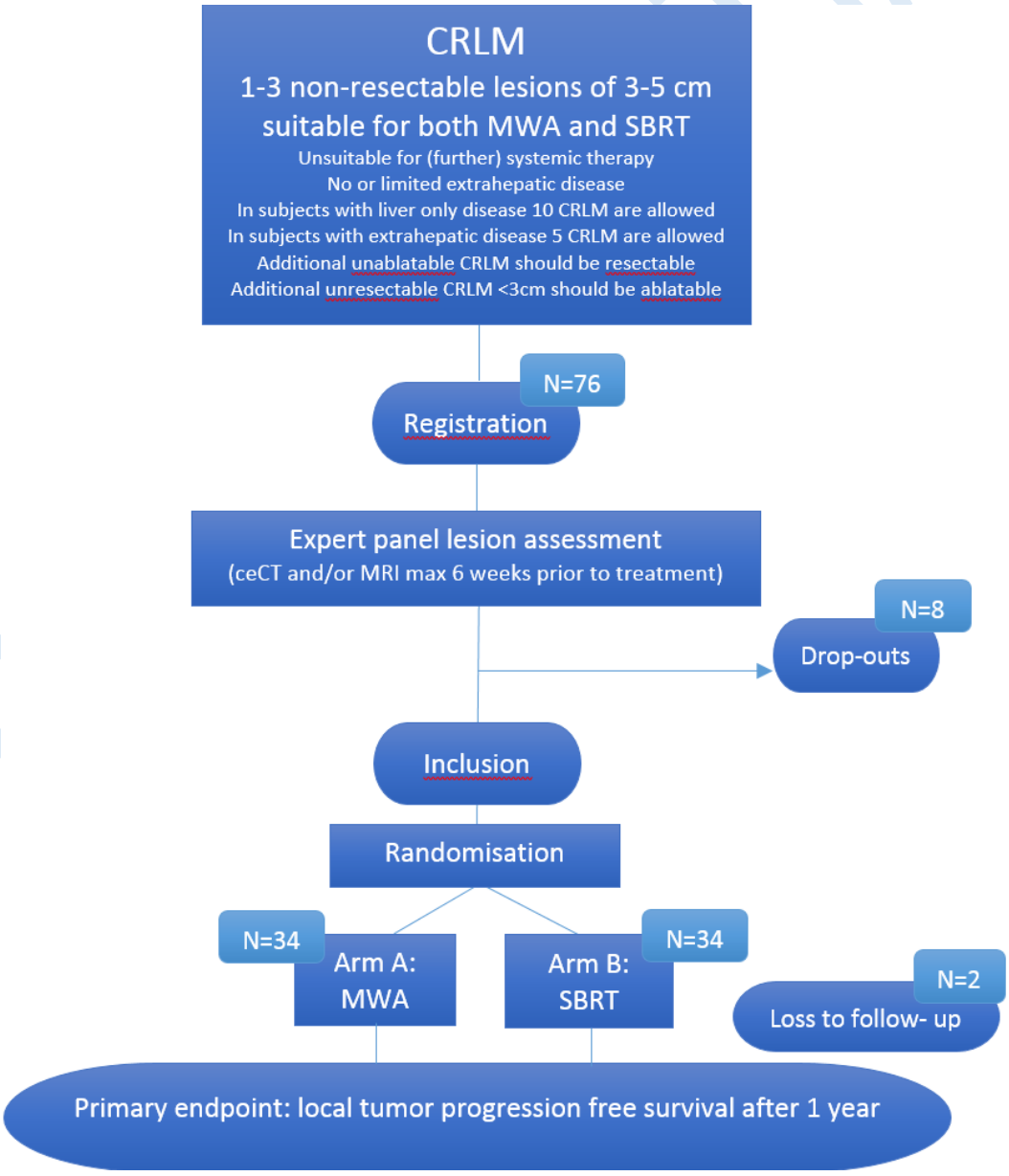
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3. STUDY DESIGN

3.1 Study design

The COLLISION XL trial is a multi-centre phase-II randomized controlled trial. In this study, we will compare 1-year LTPFS in MWA and SBRT in patients with unresectable CRLM of 3-5cm. The follow-up period will be till the date of death from any cause or at least one year after local treatment. The formal starting time of study participation will be from the date of randomization. The inclusion period is estimated to be three years.

3.1.1 Figure 1: flow chart study design



3.2 Study enrolment

Pre-registration

All patients will be discussed in local multidisciplinary liver tumour boards of participating centres. Potential candidates will be registered and undergo a routine pre-procedural work-up (which is part of standard care): total body ^{18}F-FDG PET-CT, ceCT of the abdomen, anaesthetic review (in case of MWA and/or surgery) and baseline tumour marker CEA is measured.

Registration

The patient's medical history and the functional and anatomical images will be reviewed for eligibility by an expert panel consisting of at least two interventional radiologists, two hepatobiliary surgeons and two radiotherapists. They will appoint lesions of 3-5cm that are unresectable and suitable for both MWA and SBRT as target lesions, lesions that are suitable for resection, and unresectable lesions ≤3cm that are suitable for thermal ablation. All unablatable lesions should be resectable and all unresectable lesions ≤3cm should be ablatable.

Because definitions of resectability and ablatability can vary dramatically from one centre to the other and from one specialist to the other, the local centre and the treating physicians have to agree with the panel's decision. If they disagree or feel uncomfortable with the advice from the expert panel they can either invite the experts for the procedure or refer the patient to the centre where appointed panel members are affiliated.

Enrolment

If the patient is found eligible by the expert panel, the treating physicians physicians will inform the patient about the trial. Possible risks of participating will be discussed with the candidate. If the patient is interested in participating, the treating physician will inform the investigator about the patient's interest. Thereafter, the investigator will further inform the patient about the trial and send the patient information. After the patient has had enough time for reflection (at least 7 days after receiving patient information) and has no more questions, the patient is allowed to sign the informed consent form in duplicate at home. The signed informed consents can be send back using a self-addressed envelope. After having obtained written informed consent by post, the investigator will sign both informed consent forms and send one of the two signed forms back to the patient. Subsequently, patients will be formally included. The patient should be

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scheduled to undergo the procedure within a time-frame of maximum six weeks hereafter. Patients will not receive reimbursements for participating in this study.

Patients without additional CRLM that require resection will be randomized prior to the procedure. Patients with at least 1 additional CRLM requiring resection will undergo laparoscopy or laparotomy with surgical inspection of the abdominal cavity and intraoperative ultrasound (IOUS). Following surgical inspection and IOUS the inclusion criteria need to be reconfirmed *prior to randomization*. If (1) a radical procedure is no longer considered safe or feasible, if (2) impermissible extrahepatic disease is detected, if (3) >10 CRLM are present in patients with liver only disease or >5 CRLM in patients with extrahepatic disease, or if (4) no lesion can be appointed as target lesion, the patient will be excluded from the study (drop-out). Additional unresectable CRLM of 3-5cm suitable for both MWA and SBRT will be appointed as new target lesions. Additional unresectable lesions ≤ 3 cm that are suitable for thermal ablation should be ablated and vice versa additionally detected unablatable lesions should be resected. Lesions, preprocedurally appointed as target lesions, that prove unsuitable for one treatment modality based on IOUS lose their status and should be treated with an alternate modality.

3.3 Randomization

Patients with no resectable lesions will be randomized prior to the procedure, into one of two arms, arm A (percutaneous MWA) and arm B (SBRT). Patients randomized prior to treatment will have to be treated within 4 weeks after randomization. All other patients will undergo laparotomy or laparoscopy with IOUS and surgical inspection and if still considered eligible randomized during general anaesthesia. Patients included in study arm A will undergo ultrasound guided MWA of hepatic metastases. Patients included in study arm B will undergo SBRT at a later time (two-stage procedure).

Blocked randomization with randomly selected block sizes of 4 and 6 will be performed centrally through a web-based module (CASTOR), with stratification according to extrahepatic disease and patients undergoing surgical resection. When resectable CRLMs are present, randomization will be performed while the patient is under general anaesthesia, both the experimenter and the participant will be unaware of the appointed treatment arm prior to the procedure.

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Changes in insights detected *after randomization* do not allow patient's exclusion. These patients will remain in their originally appointed group according to the intention-to-treat analysis. For example, if, after being randomized into the MWA arm, a target lesion proves unablatable during procedure, the patient will remain in arm A (MWA) even if the lesion was eventually left untreated or treated otherwise.

3.4 Surgical resection

An expert panel consisting of at least two interventional radiologists, two hepatobiliary surgeons and two radiation oncologists will determine if the CRLM are (un)resectable, according to the following criteria:

General 'resectability criteria':

- Radical resection(s) aiming at negative (R0) margins (with or without radical ablations for additional unresectable lesions) should be technically possible for all resectable CRLM;
- Radical resection(s) with or without radical ablations for additional unresectable lesions should leave a sufficient future liver remnant (>20% normal functioning liver parenchyma; >30% post-chemotherapy);
- Portal vein embolization of the (most) affected liver lobe may be considered for patients with insufficient future liver remnant;
- At least one of three hepatic veins should be preserved and both the portal venous and hepatic arterial blood flow in the future liver remnant should remain unharmed;
- The surgical field should be approachable, without extensive scar formation, major surgical adhesions and/or intestinal herniations that would entail an unacceptable procedure related risk (risk of major morbidity estimated >20%; risk of mortality estimated >5%)

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3.5 Microwave ablation

The patient's functional and anatomical images will be reviewed for eligibility by an expert panel consisting of at least two interventional radiologists, two hepatobiliary surgeons and two radiation oncologists.

General 'thermal ablatability criteria':

- Radical ablation(s) aiming at a tumour free margin of >10 mm (with or without surgical resections for additional unablatable lesions) should be technically possible for all ablatable CRLM
- Radical ablation(s) with or without surgical resections for additional unablatable lesions should leave sufficient future liver remnant (>20% normal functioning liver parenchyma; >30% post-chemotherapy);
- To preserve the major bile ducts (common, right and left hepatic duct) a sufficient distance (lesion to major bile duct) is required;
- To avoid collateral damage to the intestines a minimum distance to the stomach, small bowel and colon of 15 mm should be pursued in open procedures and respected in percutaneous procedures; the use of pneumo- or hydrodissections to shift bowels are allowed;
- Maximum total number of CRLM is 10 in patients with liver only disease and 5 in patients with extrahepatic disease;

Approach:

<u>Percutaneous MWA</u>

Patients with no resectable lesions will be randomized prior to the procedure (see chapter 3.3). Contra-indications for a percutaneous approach are proximity of critical structures. To avoid collateral damage to intestines a minimum distance to the stomach, small bowel and colon of 15 mm should be respected. Pneumo- or hydrodissections are allowed. To assess technical efficacy a ceCT (or MRI) should be made, within two weeks after the procedure to allow for completion ablations within 6 weeks for residual disease.

<u>Open MWA</u>

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Patients with resectable lesions will be randomized during open laparotomy after IOUS (see chapter 3.3). Procedures will be conducted under general anaesthesia during open laparotomy via either a subcostal or a transverse epigastric incision, based on the judgment of the surgeon performing the procedure. The abdominal cavity will be explored in order to check for extrahepatic tumour manifestations by an experienced hepatobiliary surgeon. Experienced is here defined as being a certified liver surgeon with broad expertise ((having performed and/or supervised >100 liver resections) in liver tumour resections. An intra-operative ultrasound (IOUS) to exclude additional CRLM and for final confirmation of resectability will always be performed by an experienced interventional radiologist. Experienced is defined as being a certified interventional radiologist (having performed and/or supervised >100 intraoperative ultrasound procedures). Pringel manoeuvres are not allowed.

Laparoscopic MWA

Patients with resectable lesions suitable for laparoscopy can be randomized during laparoscopy after IOUS. Procedures will be conducted under general anaesthesia. During laparoscopy the abdominal cavity will be explored and an IOUS will be performed. If the patient is still found to be eligible, the patient will be randomized during laparoscopy. Laparoscopic MWA is allowed in centres with ample experience. Postoperative care will be on the recovery and subsequently on either the surgery ward or medium care whenever deemed necessary.

Ablation procedure

If randomized to MWA the ablation is performed according to the CIRSE quality improvement guidelines with an intentional tumour free ablation margin of at least 1 cm by an experienced operator. Experienced is here defined as having a mastery degree in image-guided tumour ablation (having performed and/or supervised >100 thermal ablation procedures). The definition of a technically successful ablation is based upon the specific protocols established by the device manufacturers. Necessity for overlapping re-ablations and/or needle repositioning will be judged by the performing interventional radiologist. Postoperative care will be on the recovery and subsequently on either the surgery ward or medium care whenever deemed necessary.

Completion ablations for residual disease and re-ablations for early recurrence

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Completion ablations for residual disease or inadequate tumour-free safety margins are allowed if detected on cross-sectional imaging and retreated ≤6 weeks after initial treatment. The initial procedure will then be evaluated as a technically unsuccessful procedure, but if successfully re-ablated the retreated residue will not count as local tumour progression or disease recurrence with regards to LTPFS and DFS.

Disease recurrence detected >6 weeks after the initial MWA procedure will not be judged as technical failure, but as ablation site recurrence. If successfully re-ablated within 6 months after the initial treatment the ablation site recurrence will not be regarded as an event for LTPFS or DFS.

3.6 Stereotactic body radiotherapy

SBRT fractionating schedule

SBRT will be delivered in an image-guided hypofractionated scheme of 60Gy in 3, 5 or 8 fractions, prescribed to 95% of the planning target volume (PTV).

Procedure

A minimum interval of six weeks between the last course of chemotherapy and the start of radiotherapy is mandatory. In preparation for treatment delivery, all patients will undergo a planning-CT scan, and a planning MRI in case of MR guided treatment. Patients will be simulated and treated in supine position according to institutional standards for SBRT. Abdominal compression, gated treatment or breath hold may be used, but is not mandatory.

Intravenous contrast may be used during simulation; however, it will not be required. Oral contrast should be used with caution as it may interfere with the planning process, and the reproducibility during treatment delivery. Diagnostic imaging studies can be co-registered, however taking the respiratory phase in which the specific examination was performed into account. Fusion will be centred on the area of interest i.e. the CRLMs.

Definitions and contouring of target volumes and organs at risk (OAR)

For this SBRT study, the clinical tumor volume (CTV) equals the GTV. The PTV will be generated by the addition of a 3-10 mm margin around the GTV depending on institutional protocols.

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The duodenum, stomach, bowel, liver, kidneys, and spinal cord will be contoured as avoidance structures. Normal tissue structures will be contoured depending on the method of motion management. When an ITV concept is used including motion, motion should also be included in the delineation of critical structures for maximum critical dose (i.e esophagus, stomach, bowel, duodenum). The liver should be delineated on the average phase bin and not include all motion, otherwise the volume of low liver dose will be overestimated.

Radiation technique

Setup: daily online setup on liver, OAR, and/or clips.

Radiation therapy will be delivered using any high-precision SBRT technique; this can be in the form of MR guided radiotherapy, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), tomotherapy, or using multiple non-coplanar fields or arcs. Participating institutes will have to define their standard radiation delivery technique(s) prior to the initiation of the study.

Treatment planning, dose calculation and set-up verification

Prescription dose shall be according to the following specifications:

- The PTV will receive a dose of 60Gy in 3, 5 or 8 fractions, prescribed to 95% of the PTV .
- The 5 or 8 fraction schedule will be used in case of overlap with central hilar structures, large vessels (typically the vena cava), gallbladder or in cases where underdosing the GTV/PTV is necessary due to near critical structures (esophagus, stomach, duodenum, bowel).
- In cases where underdosing the GTV/PTV is necessary due to near critical structures, the minimum coverage should be 95% of the dose (57Gy) to 95% of the PTV (otherwise a patient should not be included in the study).
- Dose inhomogeneity is allowed up to 140% (84Gy) of the prescribed dose, the hotspot must be located within the GTV.
- At least a type B dose calculation algorithm should be used for dose calculation,
- Tissue density inhomogeneity correction will be used.

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Dose constraints:

Based on the Dutch national consensus meetings of the “landelijk platform leverstereo”.

Dosis constraints	3x20Gy	5x12Gy	8x7,5Gy	EQD 2Gy
Liver (α/ß=3)	700cc sparen tot <15Gy[$]	700cc sparen tot <18Gy[$]	700cc sparen tot <22Gy[$]	≈24Gy
Spinal cord (α/ß=2)	≤18Gy	≤22Gy	≤27Gy	≈36Gy
Esophagus (α/ß=3)	≤27Gy	≤33Gy	≤40Gy	≈64.8Gy
Small bowel /stomach (α/ß=3)	≤30Gy en D5cc ≤22Gy[#]	≤36.5Gy en D5cc ≤26Gy[#]	≤44Gy en D5cc ≤33Gy[#]	≈78Gy ≈≤47Gy
Right kidney[#] (α/ß=3)	67% sparen tot <15Gy	67% sparen tot <18Gy	67% sparen tot <22Gy	≈24Gy
Chestwal[#] (α/ß=3)	30cc ≤ 30Gy geen hotspots	30cc ≤ 36Gy geen hotspots	30cc ≤ 44Gy geen hotspots	≈78Gy
Skin[#] (α/ß=3)	≤ 27Gy	≤ 32 Gy	≤ 38Gy	≈ 60Gy

[#]Soft constraints (planning objectives), no underdosage of the PTV.

Constraints used for MR guided treatment (SMART) based on volume instead of point max, and esophagus dose equal to other bowel structures:

Constraints:	3 fractions	5 fractions	8 fractions	Equivalent 2Gy
Esophagus, stomach, duodenum, (small) bowel	-V28 ≤0.1 cc -V26 ≤1 cc	-V36 ≤0.1 cc -V33 ≤1 cc	-V43 ≤0.1 cc -V40 ≤1 cc	74 Gy

Re-ablations for early recurrence

If disease recurrence is detected and treated with re-SBRT within 6 months after the initial treatment the ablation site recurrence will not be regarded as an event for LTPFS or DFS. Re-SBRT will have to be performed with sufficiently high doses to be considered ablative.

Radiation toxicity

All radiation-associated early and late toxicity will be scored according to the common toxicity criteria (CTCAE toxicity criteria version 5.0).

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3.7 Follow-up

Follow-up imaging and laboratory tests should be identical in both treatment arms to avoid bias with regards to both the primary and secondary endpoints such as distant progression.

A ceCT-scan should be performed within four weeks after the initial treatment in both arms. Necessity for a completion-procedure in the MWA arm, within 6 weeks following the initial procedure, will be judged by the performing interventional radiologist. As it is impossible to determine technical success after SBRT within 4 weeks, this ceCT scan will become the new reference ceCT to determine future local tumor progression.

Conferring to national guidelines follow-up will include imaging (table 2), laboratory tests (albumin, AST, ALT, AF, γ-GT, LDH, bilirubin) including tumour markers (CEA) and clinical examination every 3 months for the first year and every 6 months hereafter. For arm A, within 4 weeks after initial treatment a ceCT will be performed to allow for completion ablation. The follow-up that usually takes place at 6 months will be done at 5 months to allow for repeat ablation in case of lesion recurrence within 6 months after initial treatment. Quality of life questionnaires will be assessed at baseline and every 3 months for the first year.

Table 2: Follow-up imaging

	Baseline	0-4 weeks	2-4 months	4-5 months	8-9 months	11-12 months
Imaging	ceCT, ceMRI and/or ^{18}F-FDG PET-CT	ceCT	ceCT, ceMRI and/or ^{18}F-FDG PET-CT	ceCT, ceMRI and/or ^{18}F-FDG PET-CT	ceCT, ceMRI and/or ^{18}F-FDG PET-CT	ceCT, ceMRI and/or ^{18}F-FDG PET-CT
Lab	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA	albumin, AST, ALT, AF, GGT, LDH, bilirubin, CEA

3.8 Recurrence suitable for retreatment

In the MWA-arm local site residue is defined as the presence of residual vital tumour tissue on the first follow-up imaging assessment. Local site recurrence is defined as the re-appearance of vital tumour tissue in direct contact with the resection margins or with the ablation site. Local site residue, local site recurrence and new CRLM suitable for local treatment will be treated as

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randomized with the technique used to treat the initial target lesion(s) when possible. If this is not possible, the best possible alternative local treatment will be chosen. All patients will be discussed in the expert panel to determine the optimal treatment modality for retreatment.

3.9 Recurrence unsuitable for radical treatment

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.

3.10 Quality-assurance and quality-control

Primary coordinating centre

The study will be coordinated by the VU University Medical Centre (VUmc) in Amsterdam responsible for collecting and analysing the data. All images will be forwarded to an appointed expert panel to assess eligibility and also for the formal assessment of tumour recurrence hereafter. A central data management organization will be responsible for the collection of clinical follow-up data, laboratory tests and quality of life questionnaires.

Participating centres

Participating centres will need to have extensive experience in the field of both hepatic surgery and thermal liver tumour ablation, they should perform at least 20 liver resections and 20 ablative procedures annually. Not all centres have the facilities for SBRT, these centres can refer patients to participating centres with the facilities and expertise for SBRT. Participating centres need to have all the regulatory certifications to perform these procedures and they are responsible for the acquisition of pre-procedural and follow-up imaging, laboratory tests and clinical controls as specified in the trial protocol.

Participating physicians

To prevent complications the participating interventional radiologists and radiation oncologists should be highly experienced. The operator performing the ablation should be highly experienced. Experienced is here defined as having a mastery degree in image-guided tumour ablation (having performed and/or supervised >100 ablation procedures). Control and

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reversibility of adverse events will be prevented and dealt with by adhering to standard protocols, by medical personnel that is familiar with the procedures and the complications to be expected. Ablation will be performed according to manufacturer's guidelines.

Quality-control

During the study the follow-up imaging data will be reviewed by the expert panel. If participating centres and/or physicians fail to produce tumour free margins of 10mm after the first ablation for the percutaneous group in >5 out of their first 10 patients (requiring direct re-ablation) they will be excluded from further study participation. If physicians have >2 local site recurrences in their first 10 procedures (based on 3-12 month follow-up imaging) they will also be excluded from further study participation.

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4. STUDY POPULATION

4.1 Population

Patients with hepatic metastasized colorectal cancer, with at least one intermediate size (3-5cm) CRLM that is unsuitable for resection. These patients will be selected in consensus with the expert panel, according to the in- and exclusion criteria as mentioned below. A total 68 patients will be randomized into one of two arms. Arm A will undergo MWA (n=34) and arm B will undergo SBRT (n=34).

4.2 Inclusion criteria

Screening must be performed no longer than 6 weeks prior to study inclusion. Subjects are eligible if they meet the following criteria:

- Histological documentation of primary colorectal tumour;
- 1-3 unresectable CRLM size 3-5 cm eligible for both MWA and SBRT (target lesions);
- Additional CRLM are allowed if considered either resectable or ablatable and <3cm
- No or limited extrahepatic disease (1 extrahepatic lesion is allowed, not including positive para-aortal lymph nodes, celiac lymph nodes, adrenal metastases, pleural carcinomatosis or peritoneal carcinomatosis);
- For subjects with liver only disease the maximum number of CRLM is 10; for subjects with limited extrahepatic disease the maximum number of CRLM is 5;
- Prior focal liver treatment is allowed
- Subjects without prior focal liver treatment should be either unsuitable for 1st line chemotherapy or have progressed under/after 1st-line chemotherapy;
- Subjects with recurrent (either local or distant-hepatic) CRLM after previous focal treatment should be unsuitable for (further) systemic therapy (further downsizing or conversion to resectable disease improbable);
- Resection for resectable lesions considered possible obtaining negative resection margins (R0) and preserving adequate future liver remnant (FLR);
- Age >18 years;
- Written informed consent

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4.3 Exclusion criteria

Subjects who meet the following criteria at the time of screening will be excluded:

- No target lesions suitable for both MWA and SBRT;
- Radical treatment unfeasible or unsafe (e.g. insufficient FLR);
- Compromised liver function (e.g. signs of portal hypertension, INR > 1,5 without use of anticoagulants, ascites);
- Pregnant or breast-feeding subjects;
- Immunotherapy ≤ 6 weeks prior to the procedure;
- Chemotherapy ≤ 6 weeks prior to the procedure;
- Severe allergy to contrast media not controlled with premedication;

Pulmonary nodules

Pulmonary nodules are considered benign whenever they contain calcium and/or fat. (333) (334) (335) Pulmonary nodules are considered suspect for metastases in case of:

- new or increasing in size (at least 20% increase in longest diameter);
- unequivocal 18F-FDG tracer-uptake;
- solitary nodule and >10mm;
- 2 - 5 nodules and at least 1 nodule of ≥8mm;
- more than 5 nodules (except for nodules which are suspect for other disease, like sarcoidosis, which will show equal imaging characteristics over the years)

Patients with >1 nodule suspect for metastases will be excluded from study participation.

4.4 Sample size calculation

Given the unknown 1-year local tumour progression (1y-LTP) rate for CRLM 3-5cm in size for both techniques, it was not possible to apply validated assumptions for both proportions. Hence a difference in 1y-LTP rate of more than one third (33%) is considered clinically relevant as it seems unlikely that a smaller difference will significantly impact overall survival. Most 1-year LTPs will either be re-ablated or patients will receive systemic chemotherapy because of the simultaneous presence of extensive disease recurrence elsewhere. In other words, unablatable local tumour progression at 1-year without recurrence at distant sites is uncommon. We therefore accept that

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a difference in 1-year LTPFS of more than one third (0.33) will reject the null hypothesis concluding that the techniques are significantly different.

In consultation with our statistician we calculated the following:

Group sample sizes of 33 in group 1 and 33 in group 2 achieve 81,059% power to detect a difference between the group proportions of -0,33. The proportion in group 1 (the treatment group) is assumed to be 0,665 under the null hypothesis and 0,3350 under the alternative hypothesis. The proportion in group 2 (the alternative treatment group) is 0,665. The test statistic used is the two-sided Z-test with unpooled variance. The significance level of the test is 0,05. To account for a 3% loss to follow-up (N_{LTFU}=2) we need to randomize 34 patients(N_R) into one of two arms

Table 2. *Sample size calculation*

Significance level (α)	*0.05*
Power (1-β)	*0.80*
Estimated proportion experimental group (P_A)	*0.335*
Estimated proportion control group (P_B)	*0,665*
Ratio control vs. experimental: m_2/m_1	*1.0*
Total sample size (N_S)	*66*
Accounting for 3% loss to follow-up after randomization (N_{LTFU})	*2*
Total number to be randomized (N_R)	*68*

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5. TREATMENT OF PATIENTS

5.1 Investigational treatment

Arm A: Microwave ablation, see paragraph 3.6 for a description

Arm B: Stereotactic body radiotherapy, see paragraph 3.7 for a description

5.2 Use of co-intervention

At study initiation, patients should report their concomitant medications to the physician. All patients are allowed adequate pain relief and oral intake as is indicated in the perioperative liver surgery protocol. Complications will be treated as indicated in all patients.

5.3 Escape treatment

There is no separate escape treatment for adverse events. See paragraph 5.2 Use of co-intervention.

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6. INVESTIGATIONAL PRODUCT

This trial does not investigate a product. Only CE marked generators, probes and other equipment will be used according to manufacturer's protocol. Therefore this chapter is not applicable.

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7. METHODS

7.1 Study parameters/endpoints

The primary and secondary study endpoints and measurements are previously described in paragraph 2.1 and 2.2.

7.2 Randomization, blinding and treatment allocation

Each participating centre will appoint at least one participating surgeon, one participating interventional radiologist and one participating radiation oncologist. A centralized expert panel consisting of two interventional radiologists, two radiation oncologists and two hepatobiliary surgeons will judge if a macroscopically radical treatment is possible for each individual patient. After workup, registration, inclusion and intra-operative eligibility reconfirmation, patients will be randomized into one of two arms; arm A: MWA and arm B: SBRT.

After study inclusion and informed consent, patients will be randomly assigned to one of the two study arms, arm A and arm B (Figure 1). Blocked randomization with randomly selected block sizes of 4 and 6 will be performed centrally through a web-based module (CASTOR), with stratification according to extrahepatic disease and patients undergoing surgical resection. The randomization will not be blinded for the study coordinators, treating physicians or patients. This means that the research group is aware of the appointed treatment arm. Therefore, there will be no need to break the randomization code. Both the experimenters (the physicians and study coordinators) and the patients are aware of the appointed treatment arm prior to the actual procedure when there are no resectable lesions. When there are resectable lesions both the experimenters (the physicians and study coordinators) and the patients are unaware of the appointed treatment arm prior to surgery.

7.3 Study procedures

7.3.1 Pre-procedure

The pre-operative workup of participants in this study is identical to standard pre-operative procedures for non-study objects. All patients will be discussed in local multidisciplinary liver tumour boards of participating centres. Potential candidates will be registered and undergo a routine pre-procedural work-up: total body ^{18}F-FDG PET-CT, ceCT of the abdomen, anaesthetic

review (for patients undergoing MWA and surgery). Contrast-enhanced Magnetic Resonance Imaging (ceMRI) will be used as problem solver. Routine workup including ceMRI plus ceCT is allowed.

The patient's medical history and the functional and anatomical images will be reviewed for eligibility by a centralized expert panel consisting of at least two interventional radiologists, two radiation oncologists and two hepatobiliary surgeons. Because definitions of resectability and ablatability can vary dramatically from one centre to the other and from one specialist to the other, the local centre and the treating physicians have to agree with the panel's decision. If they disagree or feel uncomfortable with the advice from the expert panel they can either invite the experts for the procedure or refer the patient to the centre where appointed panel members are affiliated.

After abovementioned pre-operative work-up is complete, and the patient is found eligible to participate in this study, he or she is informed about the possible study participation and additional oral and written information is provided. If the in- and exclusion criteria are met (see: chapter 3.2-3.3) and informed consent is given, the patient will be included in the study. Patients will be given at least 1 day to overthink participation in this study and sign informed consent. 3-7 days prior to MWA/surgery anticoagulants must be discontinued. Twelve hours before MWA/surgery, all patients are expected to fast conformal to standard pre-operative protocol. Standard pre-operative blood test will be extended to measure preoperative levels of renal function including sodium, potassium, ureum, creatinine and liver enzymes including AST, ALT, bilirubin, gGT, LDH as baseline value.

7.3.2 Interventional procedure

7.3.2.1 General anaesthesia

Only the patients in this study with resectable lesions beside the target lesions will receive general anaesthesia. As the resectable lesions are not investigated in this trial, standard care will be applied for these lesions. Patients randomized for percutaneous MWA will receive propofol sedation. The anaesthetic procedure of participants in this study is identical to standard procedures for non-study objects. The anaesthesiologists should be familiar with thermal

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ablation and its possible side-effects. All patients receive periprocedural anaesthesia care according to the current clinical standards: if indicated, an epidural catheter for postoperative analgesia will be inserted before induction of anaesthesia. General anaesthesia will be induced with propofol, sufentanil, and rocuronium and maintained with volatile anaesthetics supplemented with sufentanil titrated to the patients need. Patients will be monitored with pulseoxymetry, invasive and non-invasive arterial blood pressure, 12-lead ECG, temperature probe and capnography according to protocol. A defibrillation device will be present in the operating theatre at all times. All patients will routinely receive prophylactic antibiotics according to local protocol to prevent post-operative infection.

7.3.2.2 Explorative laparotomy

The surgical explorative procedure of participants in this study with resectable lesions is identical to standard procedures for non-study objects. A right subcostal incision is performed. After liver exposure the (interventional) radiologist joins the procedure. Using IOUS, an exact evaluation of maximum diameter, number and location of all lesions is performed and the definite resectability is determined. Also, the abdominal cavity is explored in order to exclude extrahepatic tumour manifestation by the surgeon (manually and visually). The safety, feasibility and preferred type of surgical resection(s) is at the discretion of the liver surgeon. The safety, feasibility and preferred type of thermal ablation(s) is at the discretion of the interventional radiologist. If eligibility is reconfirmed the study coordinator will formally randomize the patient.

7.3.2.3 Surgical resection

The surgeon will resect all lesions that are resectable. Surgical resection of hepatic metastases may comprise wedge-resections, segmentectomy or (extended)hemihepatectomy depending on the number, size and site of hepatic metastases. Complications encountered during the procedure will be carefully noted. After completion of the resection, the fascia will be closed using vicryl and the skin will be closed using monocryl or ethilon suture.

7.3.2.4 Microwave ablation

In case of randomization to arm A (MWA) appointed target lesions will be treated with thermal ablation. The preferred generator settings and probe size are at the discretion of the performing

interventional radiologist. To avoid recurrence the ablation zone should include a tumour free margin ≥10mm. The antennas will be manually placed intraoperatively using ultrasound guidance by interventional radiologists in close collaboration with surgical oncologists to avoid damage to surrounding organs and structures. If there are no resectable lesions the antenna will be placed percutaneously under ceCT guidance. The probes are connected to compatible and commercially available generators. Ablations will be performed according to the protocols provided by the manufacturers. The exact ablation zone will include the tumour plus a one centimetre tumour free margin. If necessary, the needle electrodes will be repositioned for one or more overlapping ablations. The proximity of a large portal or systemic vein or hepatic artery is no contraindication for performing the thermal ablation. The so called Pringle manoeuvre – the placement of a large hemostat to temporarily interrupt the flow of blood through both the hepatic artery and the portal vein – is not allowed given the associated complications. Needle track ablation will be performed to avoid needle track hemorrhage and possible seeding of tumour cells.

7.3.2.5 SBRT

In case of randomization to arm B (SBRT) appointed target lesions will be treated with SBRT. SBRT will be delivered in an image-guided hypofractionated scheme of 60Gy in 3, 5 or 8 fractions, prescribed to 95% of the planning target volume (PTV). Patients will be simulated and treated in supine position according to institutional standards for SBRT. Abdominal compression, gated treatment or breathhold may be used, but is not mandatory. Intravenous contrast may be used during simulation; however, it will not be required.

For this SBRT study, the clinical tumor volume (CTV) equals the GTV. The PTV will be generated by the addition of a 3-10 mm margin around the GTV depending on institutional protocols.

The duodenum, stomach, bowel, liver, kidneys, and spinal cord will be contoured as avoidance structures. Normal tissue structures will be contoured depending on the method of motion management. When an ITV concept is used including motion, motion should also be included in the delineation of critical structures (for maximum critical dose (i.e esophagus, stomach, bowel, duodenum). The liver should be delineated on the average phase bin and not include all motion, otherwise the volume of low liver dose will be overestimated.

Radiation therapy will be delivered using any high-precision SBRT technique; this can be in the form of MR guided radiotherapy, intensity-modulated radiotherapy (IMRT), volumetric

modulated arc therapy (VMAT), tomotherapy, or using multiple non-coplanar fields or arcs. Participating institutes will have to define their standard radiation delivery technique(s) prior to the initiation of the study.

7.3.3 Post-operative procedure

Post-operative care will be identical to routine post-operative care for non-study objects. To investigate safety, AE's and SAE's are captured until 90 days post-procedure. Complications are graded from 1 to 5 according to CTCAE version 5.0. After completion of the 90-day follow-up of all patients, adverse events will be described to provide an overview of the encountered complications. Percentages of incidence will be given for each type and grade of complication. Pain analysis will be performed using visual analogue scale questionnaires (VAS; appendix 1) assessed prior to, directly after and every three months after local treatment for one year; administered pain medication will be registered. Quality of life analysis will be performed using European Organisation for Research and Treatment of Cancer Quality of Life questionnaires (EORTC-QLQ-CR29, EORCT QLQ-C30, EQ-5D, and PRODISQ; appendix 2 and 3) prior to, and every three months after local treatment for 1 year. Follow-up will include regular blood samples including tumour markers, and imaging after 3, 6, 9 and 12 months and every 6 months hereafter. Patients undergoing MWA will receive additional imaging within 4 weeks after the initial procedure to allow for completion ablation.

7.4 Withdrawal of individual subjects

Subjects can withdraw from the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for medical reasons.

7.5 Replacement of individual subjects after withdrawal

Patients who withdraw after inclusion, but prior to randomization, will count as drop-outs and be replaced. Patients who prove ineligible during surgical inspection and IOUS will also count as drop-outs and be replaced. Patients who withdraw after randomization and patients who refuse routine follow-up examinations or to share results from follow-up will count as loss-to-follow-up. These patients will not be replaced.

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7.6 Follow-up of patients withdrawn from treatment

An excessive rate of withdrawals can render the study uninterpretable; therefore unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. The reason for withdrawal will be noted if available. These patients will receive routine follow-up outside this study. If more than 10% of patients withdraw their informed consent for any reason after 20% of patients have been included, the study will be terminated for being unfeasible.

7.7 Premature termination of the study

After having treated respectively 10 patients with SBRT or MWA (early analysis) and again after having treated 36 patients with SBRT or MWA (halftime analysis) the number of SAEs will be assessed. If the number of SAEs of SBRT is remarkably higher than expected, as compared to previously reported toxicity after SBRT, and as compared to MWA, the study will be ended prematurely. Vice versa, this also applies for MWA-treatment.

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8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10.4, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if, on the basis of which it appears, the disadvantages of participation are significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs) and serious adverse device effects (SADEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization (except for 'completion ablation procedures'; see below) or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- leads to a congenital anomaly or birth defect;
- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

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All SAEs that happen in the first 90-days of follow up, that are life threatening or result in death, both related and unrelated to the research, and serious adverse events that happen during complete study follow up, that are life threatening or result in death and are related (possible, probable or definite) to the research according to one of the principal investigators, will be reported within 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report. Relationship of the event to the research will be established by the primary investigator as:

1 = Unrelated (clearly not related to the research),
2 = Unlikely (doubtfully related to the research),
3 = Possible (may be related to the research),
4 = Probable (likely related to the research),
5 = Definite (clearly related to the research).

All participating clinicians will be made aware of the necessity to report (serious) adverse events to the principal investigators.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.2.3 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

To investigate safety, AE's and SAE's are captured until 90 days after the procedure. Complications are graded from 1 to 5 according to the CTCAE version 5.0. After the completion of the 90-day follow-up of all patients, adverse events will be labelled to provide an overview of the encountered complications. Incidence percentages, severity ratings and event relationships will be assessed for all adverse events.

Table 3. Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

CTCAE version 5.0 (*http://ctep.cancer.gov*)	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.
A Semi-colon indicates 'or' within the description of the grade. *Activities of Daily Living (ADL);* **Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.* ***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*	

8.2.4 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

8.3 Annual safety report

Not applicable

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Safety Committee

The investigators believe that an independent data safety and monitoring board (DSMB) is unnecessary since the treatments we are going to investigate are part of standard care.

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An independent monitor committee (Clinical Research Bureau; CRB) is appointed to safeguard the quality of all investigator-initiated studies. A quality officer from the CRB will monitor all study data according to Good Clinical Practice (GCP). The informed consent of selected individual participants will be checked. Source Data verification will be performed during onsite monitoring (to verify if all data on the Case Report Form are in accordance with the source data). The intensity of this verification is in relation to the risk associated with the intervention investigated. Data that by all means will be checked are the informed consent form, in- and exclusion criteria and the primary outcome. The monitor will also verify if all (S)AE's are reported adequately and within the time that is determined by legal rules and regulations.

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9. STATISTICAL ANALYSIS

All randomized patients will be included in the analysis of efficacy, based on a per lesion analysis. All clinicopathological and procedural variables mentioned in section 2 will be described and analysed. Continuous variables will be summarized with standard statistics including, means, standard deviations, medians and ranges. Categorical variables will be summarized with frequencies. When appropriate, box plots and cross tables will be used for descriptive statistics of continuous and categorical variables, respectively. Variables that will be taken in to account are: location, amount and size of lesions, extrahepatic disease, ablation margin after MWA and if available RAS mutation. We expect the number of missing values to be low, since the follow-up in this study is part of standard care. P-values below 0.05 will be considered significant. All calculations will be generated by statistical package for social sciences software (SPSS). Calculation of the number of patients that will be needed to address our primary endpoint with a power of 80% and a 5% type I error rate is described in section 4.4.

9.1 Primary study parameter

The primary study parameter is local tumour progression free survival (LTPFS) 1 year after treatment. The amount of patients with 1-year LTPFS will be presented in percentages per treatment arm. One year LTPFS rates will be compared between MWA and SBRT by a Chi square test.

9.2 Secondary study parameters

OS and DFS will be estimated by the Kaplan-Meier method with corresponding two sided 95% CIs for survival proportions. Differences in survival will be calculated using the log-rank test. For determining hazard ratios (HR) a Cox regression model will be used. Potential differences between the baseline arms will be corrected using a multivariate Cox regression model.

To investigate safety, AEs and SAEs are captured until 90 days post-procedure. Complications are graded from 1 to 5 according to CTCAE *version* 5.0. After completion of the 90-day follow-up of

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all patients, adverse events will be described to provide an overview of the encountered complications. Percentages of incidence will be given for each type and grade of complication.

Pain analysis will be performed using visual analogue scale questionnaires (VAS) assessed prior to, directly after and every three months after local treatment for 1 year; administered pain medication will be registered.

Quality of life analysis of patients included in the trial will be included as one of the secondary objectives of this study. Patients who complete the quality of life questionnaires at baseline and at least once during treatment and follow-up can be included in the analysis. The change between the two arms in quality of life will be compared with linear mixed models.

Direct and indirect total cost of care for both treatment arms will be registered in the cost-effectiveness data collection matrix (see appendix). Based on this matrix a cost–utility analysis, measured in terms of years of full health lived, using quality-adjusted life years will be prospectively calculated. Cost-effectiveness will be expressed as an incremental cost-effectiveness ratio (ICER), the ratio of change in costs to the change in effects.

9.3 Interim analysis

No interim analysis will be performed

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (336) (64th version, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts such as Good Clinical Practice.

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10.2 Recruitment and consent

Patients will be recruited and informed by the treating physician and the trial coordinators. Patients eligible for inclusion, will be further informed about the study and associated procedures preferably by the local principal investigators. If this is not possible for practical reasons, the study coordinator, local treating physician or a study nurse will inform patients. The informed consent document will be used to explain risks and benefits of study participation in simple terms and should be obtained before the patient is entered into the study. Section 3.2 shows more detailed recruitment and consent information.

10.3 Objection by minors or incapacitated subjects

Not applicable.

10.4 Benefits and risks assessment, group relatedness

For CRLM <3cm multiple studies have shown that thermal ablation is associated with a good local control rate. For unresectable CRLM up to 3cm this is a good alternative for resection. However for unresectable CRLM 3-5cm it is uncertain what the best treatment option is. Multiple prospective studies examining the local control rate of RFA and MWA of liver lesions that have also taken the size of the lesions into account have determined that local control rate significantly decreases to <80% with increasing tumour size >3cm. One year local control rate for SBRT varies a lot between studies, from 50% to 95%, with some studies showing that tumour volume had no influence on the local control rate. While other studies suggested that local control rate decreased with increasing tumour volume. Both MWA as SBRT are part of standard care and have a low complication rate.

No randomized controlled trials comparing SBRT to MWA have been performed yet. By participating in this study, patients will agree to undergo standard care in the form of SBRT or MWA and they will help to determine what treatment option is preferable considering safety and efficacy. Thereby possibly improving care for future patients with unresectable CRLM 3-5cm.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

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The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 1st July 2015). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives

Patients enrolled in this study will not receive and incentives.

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11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be handled confidentially. The collected data will be storaged in CASTOR. A subject identification code is used to link the data to the subject. A code is generated by CASTOR for each individual which is not based on the patient's last name. The study coordinators safeguard the key to the code. The handling of personal data will comply with the General Data Protection Regulation (in Dutch: De algemene verordening gegevensbescherming, AVG). The project leader (M.R. Meijerink) will keep the source data for 15 years.

11.2 Randomization

Randomization is centralized and performed through a web-based module, which is accessible 7 days a week, 24 hours per day. The study number and randomization arm need to be documented in patient's medical file as well as a copy of written informed consent.

11.3 Monitoring and Quality Assurance

The Clinical Research Bureau (CRB) of VUmc will monitor the safety of the trial and the storage of the data. Even if the safety parameters monitored are not directly related to efficacy, a CRB might need access to unblinded efficacy information to perform a risk/benefit assessment in order to weigh possible safety disadvantages against a possible gain in efficacy. Other reasons for monitoring efficacy might be for futility, checking the assumptions for sample size calculation or whether criteria for early stopping are met.

11.4 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

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11.5 Start of the study and annual progress report

The sponsor will notify the accredited METC and the competent authority of the start of the study. The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.6 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.7 Public disclosure and publication policy

After completion of the study and analysis of the data, the results will be made publicly without restriction, independent of the outcome. They will be submitted for publication to an international peer-reviewed journal. The principal investigators and study coordinators will prepare the manuscript together with those who substantially contributed to the study. Being a (co-)investigator on this trial protocol does not automatically result in a co-authorship of the manuscript reporting the study results.

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12. STRUCTURED RISK ANALYSIS

Based on the NFU report and mandatory since the 1st of January 2011, an additional risk-classification is provided. In this chapter, the additional risks for subjects are discussed in line with the checklist and a risk-classification will be formulated with a proposed monitoring policy during this study.

12.1 Summary of known and potential risks

Both these techniques are registered, are part of standard therapy and will be used within the indication. We will give a short overview of possible complications.

Microwave ablation

MWA is considered a minimally invasive and well-tolerated technique. In a retrospective multicentre study by Livraghi et al, they looked at complications in 736 patients treated with MWA. No mortality occurred and major complications occurred in 22 patients (2.9%), minor complications in 7.3%.

Complications related to probe placement:

- Bleeding (0.7%)
- Infection
- Tumour seeding (0.3% percutaneous, 0% open); “hot withdrawal” is used to minimize this complications

Complications related to thermal therapy

- Nontarget thermal damage: especially gallbladder, bile ducts (4.2%) and bowel
- Postablation syndrome: low-grade fever, malaise, chills, myalgia, delayed pain, nausea and vomiting
- Hepatic vascular damage
- Liver failure (2,1%)

Stereotactic body radiotherapy

SBRT is considered a non-invasive technique with a low complication rate. A systematic review by Petrelli et al, found grade 1-2 liver toxicity in 30,7% and grade 3-4 liver toxicity in 8.7%, liver

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failure in 0.6% and treatment related deaths in 0.4%. No radiation induced liver disease (RILD) has been reported.

Complications related to SBRT:

- Liver toxicity
- Nausea, diarrhea and fatigue
- Skin reactions
- Gastrointestinal toxicity (including ulceration or perforation of bowels, this is rare)

12.2 Synthesis

Based on the abovementioned information, the estimated risk for study subjects is divided into a “direct risk” based on the risks of undergoing the ablation procedure and an “indirect risk” based on the possibility of having local site residue or recurrence with associated burden and the risk of a worse oncological outcome . It should be noted that we aim to reduce this risk by strict follow-up regimes, so that, in case of recurrent disease, rapid re-intervention can be performed for all patients.

The direct risk is classified as low, since the number and severity of complications caused by MWA and SBRT are expected to be low.

Given the comparable local control rate for CRLM 3-5cm for SBRT and MWA, and the strict follow-up regime for rapid re-intervention when necessary, the indirect risk is classified as low.

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13. REFERENCES

Uncategorized References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917.

2. Belinson S, Chopra R, Yang Y, Shankaran V, Aronson N. Local Hepatic Therapies for Metastases to the Liver From Unresectable Colorectal Cancer. AHRQ Comparative Effectiveness Reviews. Rockville (MD)2012.

3. Cirocchi R, Trastulli S, Boselli C, Montedori A, Cavaliere D, Parisi A, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database Syst Rev. 2012;6:CD006317.

4. Bengmark S, Hafstrom L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer. 1969;23(1):198-202.

5. Goldberg RM. Therapy for metastatic colorectal cancer. Oncologist. 2006;11(9):981-7.

6. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42.

7. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818-25; discussion 25-7.

8. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438-47; discussion 47-50.

CONFIDENTIAL

9. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg. 2006;93(4):465-74.

10. Wei AC, Greig PD, Grant D, Taylor B, Langer B, Gallinger S. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006;13(5):668-76.

11. Mulier S, Ruers T, Jamart J, Michel L, Marchal G, Ni Y. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? An update. Dig Surg. 2008;25(6):445-60.

12. Abitabile P, Hartl U, Lange J, Maurer CA. Radiofrequency ablation permits an effective treatment for colorectal liver metastasis. Eur J Surg Oncol. 2007;33(1):67-71.

13. Ahmad A, Chen SL, Kavanagh MA, Allegra DP, Bilchik AJ. Radiofrequency ablation of hepatic metastases from colorectal cancer: are newer generation probes better? Am Surg. 2006;72(10):875-9.

14. Aksoy E, Aliyev S, Taskin HE, Birsen O, Mitchell J, Siperstein A, et al. Clinical scenarios associated with local recurrence after laparoscopic radiofrequency thermal ablation of colorectal liver metastases. Surgery. 2013;154(4):748-52; discussion 52-4.

15. Al-Asfoor A, Fedorowicz Z, Lodge M. Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases. Cochrane Database Syst Rev. 2008(2):CD006039.

16. Amersi FF, McElrath-Garza A, Ahmad A, Zogakis T, Allegra DP, Krasne R, et al. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. Arch Surg. 2006;141(6):581-7; discussion 7-8.

17. Andreano A, Galimberti S, Franza E, Knavel EM, Sironi S, Lee FT, et al. Percutaneous microwave ablation of hepatic tumors: prospective evaluation of postablation syndrome and postprocedural pain. J Vasc Interv Radiol. 2014;25(1):97-105 e1-2.

CONFIDENTIAL

18. Ayav A, Germain A, Marchal F, Tierris I, Laurent V, Bazin C, et al. Radiofrequency ablation of unresectable liver tumors: factors associated with incomplete ablation or local recurrence. Am J Surg. 2010;200(4):435-9.

19. Azzarello G, Lanteri R, Gresta S, Rapisarda C, Racalbuto A, Di Cataldo A, et al. Thermic ablation with RF of liver metastases from colorectal cancer. Hepatogastroenterology. 2003;50 Suppl 2:ccv-ccvii.

20. Babawale SN, Jensen TM, Frokjaer JB. Long-term survival following radiofrequency ablation of colorectal liver metastases: A retrospective study. World J Gastrointest Surg. 2015;7(3):33-8.

21. Bachar GN, Greif F, Mor E, Tur-Kaspa R, Belenky A. Radiofrequency ablation for the management of liver tumors. Isr Med Assoc J. 2003;5(7):496-500.

22. Bai H, Huangz X, Jing L, Zeng Q, Han L. The effect of radiofrequency ablation vs. liver resection on survival outcome of colorectal liver metastases (CRLM): a meta-analysis. Hepatogastroenterology. 2015;62(138):373-7.

23. Baldwin K, Katz SC, Rubin A, Somasundar P. Bipolar radiofrequency ablation of liver tumors: technical experience and interval follow-up in 22 patients with 33 ablations. J Surg Oncol. 2012;106(7):905-10.

24. Bale R, Widmann G, Schullian P, Haidu M, Pall G, Klaus A, et al. Percutaneous stereotactic radiofrequency ablation of colorectal liver metastases. Eur Radiol. 2012;22(4):930-7.

25. Basdanis G, Michalopoulos A, Papadopoulos V, Tzeveleki I, Efthimiadis C, Kosmidis C, et al. Clinical short-term results of radiofrequency ablation in patients with liver metastases from colorectal cancer. Tech Coloproctol. 2004;8 Suppl 1:s187-9.

CONFIDENTIAL

26. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol. 2005;23(7):1358-64.

27. Berber E, Senagore A, Remzi F, Rogers S, Herceg N, Casto K, et al. Laparoscopic radiofrequency ablation of liver tumors combined with colorectal procedures. Surg Laparosc Endosc Percutan Tech. 2004;14(4):186-90.

28. Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. Ann Surg Oncol. 2008;15(10):2757-64.

29. Berber E, Siperstein AE. Perioperative outcome after laparoscopic radiofrequency ablation of liver tumors: an analysis of 521 cases. Surg Endosc. 2007;21(4):613-8.

30. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol. 2011;21(12):2584-96.

31. Bhardwaj N, Strickland AD, Ahmad F, Dennison AR, Lloyd DM. Liver ablation techniques: a review. Surg Endosc. 2010;24(2):254-65.

32. Bilchik AJ, Rose DM, Allegra DP, Bostick PJ, Hsueh E, Morton DL. Radiofrequency ablation: a minimally invasive technique with multiple applications. Cancer J Sci Am. 1999;5(6):356-61.

33. Birsen O, Aliyev S, Aksoy E, Taskin HE, Akyuz M, Karabulut K, et al. A critical analysis of postoperative morbidity and mortality after laparoscopic radiofrequency ablation of liver tumors. Ann Surg Oncol. 2014;21(6):1834-40.

34. Bleicher RJ, Allegra DP, Nora DT, Wood TF, Foshag LJ, Bilchik AJ. Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. Ann Surg Oncol. 2003;10(1):52-8.

CONFIDENTIAL

35. Blokhuis TJ, van der Schaaf MC, van den Tol MP, Comans EF, Manoliu RA, van der Sijp JR. Results of radio frequency ablation of primary and secondary liver tumors: long-term follow-up with computed tomography and positron emission tomography-18F-deoxyfluoroglucose scanning. Scand J Gastroenterol Suppl. 2004(241):93-7.

36. Blusse van Oud-Alblas M, Fioole B, Jansen MC, van Duijnhoven FH, van Hillegersberg R, Rijken AM, et al. [Radiofrequency ablation of colorectal metastases to the liver: results since the first application in the Netherlands]. Ned Tijdschr Geneeskd. 2008;152(15):880-6.

37. Bonastre J, De Baere T, Elias D, Evrard S, Rouanet P, Bazin C, et al. Cost of radiofrequency ablation in the treatment of hepatic malignancies. Gastroenterol Clin Biol. 2007;31(10):828-35.

38. Buell JF, Thomas MT, Rudich S, Marvin M, Nagubandi R, Ravindra KV, et al. Experience with more than 500 minimally invasive hepatic procedures. Ann Surg. 2008;248(3):475-86.

39. Buscarini E, Buscarini L. Radiofrequency thermal ablation with expandable needle of focal liver malignancies: complication report. Eur Radiol. 2004;14(1):31-7.

40. Carrafiello G, Lagana D, Ianniello A, Dionigi G, Novario R, Recaldini C, et al. Post-radiofrequency ablation syndrome after percutaneous radiofrequency of abdominal tumours: one centre experience and review of published works. Australas Radiol. 2007;51(6):550-4.

41. Casaril A, Abu Hilal M, Harb A, Campagnaro T, Mansueto G, Nicoli N. The safety of radiofrequency thermal ablation in the treatment of liver malignancies. Eur J Surg Oncol. 2008;34(6):668-72.

42. Cassera MA, Potter KW, Ujiki MB, Swanstrom LL, Hansen PD. Computed tomography (CT)-guided versus laparoscopic radiofrequency ablation: a single-institution comparison of morbidity rates and hospital costs. Surg Endosc. 2011;25(4):1088-95.

43. Chan RP, Asch M, Kachura J, Ho CS, Greig P, Langer B, et al. Radiofrequency ablation of malignant hepatic neoplasms. Can Assoc Radiol J. 2002;53(5):272-8.

CONFIDENTIAL

44. Chen MH, Yang W, Yan K, Gao W, Dai Y, Wang YB, et al. Treatment efficacy of radiofrequency ablation of 338 patients with hepatic malignant tumor and the relevant complications. World J Gastroenterol. 2005;11(40):6395-401.

45. Chen MH, Yang W, Yan K, Zou MW, Solbiati L, Liu JB, et al. Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients--mathematic model, overlapping mode, and electrode placement process. Radiology. 2004;232(1):260-71.

46. Cheng J, Glasgow RE, O'Rourke RW, Swanstrom LL, Hansen PD. Laparoscopic radiofrequency ablation and hepatic artery infusion pump placement in the evolving treatment of colorectal hepatic metastases. Surg Endosc. 2003;17(1):61-7.

47. Chhabra DG, Shah RC, Parikh V, Jagannath P. Radiofrequency ablation of liver tumors: experience with open and percutaneous approach. Indian J Gastroenterol. 2006;25(2):66-70.

48. Chopra S, Dodd GD, 3rd, Chanin MP, Chintapalli KN. Radiofrequency ablation of hepatic tumors adjacent to the gallbladder: feasibility and safety. AJR Am J Roentgenol. 2003;180(3):697-701.

49. Chow DH, Sinn LH, Ng KK, Lam CM, Yuen J, Fan ST, et al. Radiofrequency ablation for hepatocellular carcinoma and metastatic liver tumors: a comparative study. J Surg Oncol. 2006;94(7):565-71.

50. Choy PY, Koea J, McCall J, Holden A, Osbourne M. The role of radiofrequency ablation in the treatment of primary and metastatic tumours of the liver: initial lessons learned. N Z Med J. 2002;115(1159):U128.

51. Crucitti A, Danza FM, Antinori A, Vincenzo A, Pirulli PG, Bock E, et al. Radiofrequency thermal ablation (RFA) of liver tumors: percutaneous and open surgical approaches. J Exp Clin Cancer Res. 2003;22(4 Suppl):191-5.

CONFIDENTIAL

52. Crucitti A, Danza FM, Pirulli PG, Antinori A, Antonacci V, La Greca A, et al. Radiofrequency thermal ablation (RFA) of liver tumors: open surgical or percutaneous approach? J Chemother. 2004;16 Suppl 5:82-5.

53. Curley SA. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? Ann Surg Oncol. 2008;15(1):11-3.

54. Curley SA. Radiofrequency ablation of malignant liver tumors. Ann Surg Oncol. 2003;10(4):338-47.

55. Curley SA, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, et al. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg. 1999;230(1):1-8.

56. Curley SA, Marra P, Beaty K, Ellis LM, Vauthey JN, Abdalla EK, et al. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Ann Surg. 2004;239(4):450-8.

57. Cuschieri A, Bracken J, Boni L. Initial experience with laparoscopic ultrasound-guided radiofrequency thermal ablation of hepatic tumours. Endoscopy. 1999;31(4):318-21.

58. de Baere T, Elias D, Dromain C, Din MG, Kuoch V, Ducreux M, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR Am J Roentgenol. 2000;175(6):1619-25.

59. De Baere T, Elias D, Ducreux M, Dromain C, Kuach V, Gamal El Din M, et al. [Percutaneous radiofrequency ablation of hepatic metastases. Preliminary experience]. Gastroenterol Clin Biol. 1999;23(11):1128-33.

60. de Baere T, Risse O, Kuoch V, Dromain C, Sengel C, Smayra T, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. AJR Am J Roentgenol. 2003;181(3):695-700.

CONFIDENTIAL

61. de Jong MC, van Vledder MG, Ribero D, Hubert C, Gigot JF, Choti MA, et al. Therapeutic efficacy of combined intraoperative ablation and resection for colorectal liver metastases: an international, multi-institutional analysis. J Gastrointest Surg. 2011;15(2):336-44.

62. de Leur K, Huisman F, Gobardhan PD, Kint PA, Wijsman JH, Ten Tije AJ, et al. [Treatment of colorectal liver metastasis at a regional hospital versus a university medical centre]. Ned Tijdschr Geneeskd. 2013;157(34):A6417.

63. de Meijer VE, Verhoef C, Kuiper JW, Alwayn IP, Kazemier G, Ijzermans JN. Radiofrequency ablation in patients with primary and secondary hepatic malignancies. J Gastrointest Surg. 2006;10(7):960-73.

64. Decadt B, Siriwardena AK. Radiofrequency ablation of liver tumours: systematic review. Lancet Oncol. 2004;5(9):550-60.

65. Desolneux G, Vara J, Razafindratsira T, Isambert M, Brouste V, McKelvie-Sebileau P, et al. Patterns of complications following intraoperative radiofrequency ablation for liver metastases. HPB (Oxford). 2014;16(11):1002-8.

66. Dexiang Z, Li R, Ye W, Haifu W, Yunshi Z, Qinghai Y, et al. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. Ann Surg Oncol. 2012;19(9):2860-8.

67. Eisele RM, Neumann U, Neuhaus P, Schumacher G. Open surgical is superior to percutaneous access for radiofrequency ablation of hepatic metastases. World J Surg. 2009;33(4):804-11.

68. Eisele RM, Zhukowa J, Chopra S, Schmidt SC, Neumann U, Pratschke J, et al. Results of liver resection in combination with radiofrequency ablation for hepatic malignancies. Eur J Surg Oncol. 2010;36(3):269-74.

CONFIDENTIAL

69. Elias D, Baton O, Sideris L, Boige V, Malka D, Liberale G, et al. Hepatectomy plus intraoperative radiofrequency ablation and chemotherapy to treat technically unresectable multiple colorectal liver metastases. J Surg Oncol. 2005;90(1):36-42.

70. Elias D, Baton O, Sideris L, Matsuhisa T, Pocard M, Lasser P. Local recurrences after intraoperative radiofrequency ablation of liver metastases: a comparative study with anatomic and wedge resections. Ann Surg Oncol. 2004;11(5):500-5.

71. Elias D, De Baere T, Smayra T, Ouellet JF, Roche A, Lasser P. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. Br J Surg. 2002;89(6):752-6.

72. Elias D, Goharin A, El Otmany A, Taieb J, Duvillard P, Lasser P, et al. Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. Eur J Surg Oncol. 2000;26(8):763-9.

73. Erce C, Parks RW. Interstitial ablative techniques for hepatic tumours. Br J Surg. 2003;90(3):272-89.

74. Evrard S, Becouarn Y, Fonck M, Brunet R, Mathoulin-Pelissier S, Picot V. Surgical treatment of liver metastases by radiofrequency ablation, resection, or in combination. Eur J Surg Oncol. 2004;30(4):399-406.

75. Evrard S, Rivoire M, Arnaud J, Lermite E, Bellera C, Fonck M, et al. Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. Br J Surg. 2012;99(4):558-65.

76. Fisichella R, Sparta D, Berretta S. Combined microwave thermal ablation and liver resection for single step treatment of otherwise unresectable colorectal liver metastases; a monoistitutional experiences. Eur Rev Med Pharmacol Sci. 2015;19(2):180-1.

CONFIDENTIAL

77. Fox JP, Gustafson J, Desai MM, Hellan M, Thambi-Pillai T, Ouellette J. Short-term outcomes of ablation therapy for hepatic tumors: evidence from the 2006-2009 nationwide inpatient sample. Ann Surg Oncol. 2012;19(12):3677-86.

78. Garrean S, Hering J, Helton WS, Espat NJ. A primer on transarterial, chemical, and thermal ablative therapies for hepatic tumors. Am J Surg. 2007;194(1):79-88.

79. Garrean S, Hering J, Saied A, Helton WS, Espat NJ. Radiofrequency ablation of primary and metastatic liver tumors: a critical review of the literature. Am J Surg. 2008;195(4):508-20.

80. Gazelle GS, McMahon PM, Beinfeld MT, Halpern EF, Weinstein MC. Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection. Radiology. 2004;233(3):729-39.

81. Geller DA, Tsung A, Marsh JW, Dvorchik I, Gamblin TC, Carr BI. Outcome of 1000 liver cancer patients evaluated at the UPMC Liver Cancer Center. J Gastrointest Surg. 2006;10(1):63-8.

82. Geyik S, Akhan O, Abbasoglu O, Akinci D, Ozkan OS, Hamaloglu E, et al. Radiofrequency ablation of unresectable hepatic tumors. Diagn Interv Radiol. 2006;12(4):195-200.

83. Gillams AR. Liver ablation therapy. Br J Radiol. 2004;77(921):713-23.

84. Gillams AR, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol. 2009;19(5):1206-13.

85. Gillams AR, Lees WR. Radiofrequency ablation of colorectal liver metastases. Abdom Imaging. 2005;30(4):419-26.

86. Gillams AR, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. Eur Radiol. 2004;14(12):2261-7.

CONFIDENTIAL

87. Gillams AR, Lees WR. Five-year survival following radiofrequency ablation of small, solitary, hepatic colorectal metastases. J Vasc Interv Radiol. 2008;19(5):712-7.

88. Giorgio A, Tarantino L, de Stefano G, Coppola C, Ferraioli G. Complications after percutaneous saline-enhanced radiofrequency ablation of liver tumors: 3-year experience with 336 patients at a single center. AJR Am J Roentgenol. 2005;184(1):207-11.

89. Goldberg SN, Gazelle GS, Compton CC, Mueller PR, Tanabe KK. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. Cancer. 2000;88(11):2452-63.

90. Gomez Senent S, Gomez Raposo C, Mancenido Marcos N, Martin Chavarri S, Carrion Alonso G, Olveira Martin A, et al. Radiofrequency ablation for hepatocellular carcinoma and liver metastases: experience in Hospital La Paz. Clin Transl Oncol. 2006;8(9):688-91.

91. Govaert KM, van Kessel CS, Lolkema M, Ruers TJ, Borel Rinkes IH. Does Radiofrequency Ablation Add to Chemotherapy for Unresectable Liver Metastases? Curr Colorectal Cancer Rep. 2012;8(2):130-7.

92. Gravante G, Ong SL, Metcalfe MS, Strickland A, Dennison AR, Lloyd DM. Hepatic microwave ablation: a review of the histological changes following thermal damage. Liver Int. 2008;28(7):911-21.

93. Gravante G, Overton J, Sorge R, Bhardwaj N, Metcalfe MS, Lloyd DM, et al. Radiofrequency ablation versus resection for liver tumours: an evidence-based approach to retrospective comparative studies. J Gastrointest Surg. 2011;15(2):378-87.

94. Greve JW. Alternative techniques for the treatment of colon carcinoma metastases in the liver: current status in The Netherlands. Scand J Gastroenterol Suppl. 2001(234):77-81.

95. Gwak JH, Oh BY, Lee RA, Chung SS, Kim KH. Clinical applications of radio-frequency ablation in liver metastasis of colorectal cancer. J Korean Soc Coloproctol. 2011;27(4):202-10.

CONFIDENTIAL

96. Hager ED, Dziambor H, Hohmann D, Gallenbeck D, Stephan M, Popa C. Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Res. 1999;19(4C):3403-8.

97. Hamada A, Yamakado K, Nakatsuka A, Uraki J, Kashima M, Takaki H, et al. Radiofrequency ablation for colorectal liver metastases: prognostic factors in non-surgical candidates. Jpn J Radiol. 2012;30(7):567-74.

98. Hammill CW, Billingsley KG, Cassera MA, Wolf RF, Ujiki MB, Hansen PD. Outcome after laparoscopic radiofrequency ablation of technically resectable colorectal liver metastases. Ann Surg Oncol. 2011;18(7):1947-54.

99. Hildebrand P, Kleemann M, Roblick U, Mirow L, Birth M, Bruch HP. Laparoscopic radiofrequency ablation of unresectable hepatic malignancies: indication, limitation and results. Hepatogastroenterology. 2007;54(79):2069-72.

100. Hildebrand P, Kleemann M, Roblick UJ, Mirow L, Birth M, Leibecke T, et al. Radiofrequency-ablation of unresectable primary and secondary liver tumors: results in 88 patients. Langenbecks Arch Surg. 2006;391(2):118-23.

101. Hildebrand P, Leibecke T, Kleemann M, Mirow L, Birth M, Bruch HP, et al. Influence of operator experience in radiofrequency ablation of malignant liver tumours on treatment outcome. Eur J Surg Oncol. 2006;32(4):430-4.

102. Hofer S, Oberholzer C, Beck S, Looser C, Ludwig C. Ultrasound-guided radiofrequency ablation (RFA) for inoperable gastrointestinal liver metastases. Ultraschall Med. 2008;29(4):388-92.

103. Hoffman AL, Wu SS, Obaid AK, French SW, Lois J, McMonigle M, et al. Histologic evaluation and treatment outcome after sequential radiofrequency ablation and hepatic resection for primary and metastatic tumors. Am Surg. 2002;68(12):1038-43.

CONFIDENTIAL

104. Hompes D, Prevoo W, Ruers T. Radiofrequency ablation as a treatment tool for liver metastases of colorectal origin. Cancer Imaging. 2011;11:23-30.

105. Hompes R, Fieuws S, Aerts R, Thijs M, Penninckx F, Topal B. Results of single-probe microwave ablation of metastatic liver cancer. Eur J Surg Oncol. 2010;36(8):725-30.

106. Howard JH, Tzeng CW, Smith JK, Eckhoff DE, Bynon JS, Wang T, et al. Radiofrequency ablation for unresectable tumors of the liver. Am Surg. 2008;74(7):594-600; discussion -1.

107. Hubert C, Gras J, Goffette P, Grajeda JM, Van Beers BE, Laurence A, et al. Percutaneous and surgical radiofrequency ablation of liver malignancies: a single institutional experience. Acta Gastroenterol Belg. 2007;70(2):188-94.

108. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. Arch Surg. 2002;137(4):422-6; discussion 7.

109. Ierardi AM, Floridi C, Fontana F, Chini C, Giorlando F, Piacentino F, et al. Microwave ablation of liver metastases to overcome the limitations of radiofrequency ablation. Radiol Med. 2013;118(6):949-61.

110. Izzo F. Other thermal ablation techniques: microwave and interstitial laser ablation of liver tumors. Ann Surg Oncol. 2003;10(5):491-7.

111. Jagad RB, Koshariya M, Kawamoto J, Papastratis P, Kefalourous H, Patris V, et al. Laparoscopic microwave ablation of liver tumors: our experience. Hepatogastroenterology. 2008;55(81):27-32.

112. Jakobs TF, Hoffmann RT, Trumm C, Reiser MF, Helmberger TK. Radiofrequency ablation of colorectal liver metastases: mid-term results in 68 patients. Anticancer Res. 2006;26(1B):671-80.

113. Jaskolka JD, Asch MR, Kachura JR, Ho CS, Ossip M, Wong F, et al. Needle tract seeding after radiofrequency ablation of hepatic tumors. J Vasc Interv Radiol. 2005;16(4):485-91.

CONFIDENTIAL

114. Jiang HC, Liu LX, Piao DX, Xu J, Zheng M, Zhu AL, et al. Clinical short-term results of radiofrequency ablation in liver cancers. World J Gastroenterol. 2002;8(4):624-30.

115. Jiao LR, Hansen PD, Havlik R, Mitry RR, Pignatelli M, Habib N. Clinical short-term results of radiofrequency ablation in primary and secondary liver tumors. Am J Surg. 1999;177(4):303-6.

116. Jones C, Badger SA, Ellis G. The role of microwave ablation in the management of hepatic colorectal metastases. Surgeon. 2011;9(1):33-7.

117. Joosten J, Jager G, Oyen W, Wobbes T, Ruers T. Cryosurgery and radiofrequency ablation for unresectable colorectal liver metastases. Eur J Surg Oncol. 2005;31(10):1152-9.

118. Kanellos I, Demetriades H, Blouhos K, Tsachalis T, Pramateftakis MG, Betsis D. Radio-frequency ablation of hepatic metastases from colorectal cancer. Tech Coloproctol. 2004;8 Suppl 1:s119-22.

119. Karanicolas PJ, Jarnagin WR, Gonen M, Tuorto S, Allen PJ, DeMatteo RP, et al. Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases. JAMA Surg. 2013;148(7):597-601.

120. Kele PG, de Jong KP, van der Jagt EJ. Increase in volume of ablation zones during follow-up is highly suggestive of ablation site recurrence in colorectal liver metastases treated with radiofrequency ablation. J Vasc Interv Radiol. 2012;23(4):537-44.

121. Kennedy TJ, Cassera MA, Khajanchee YS, Diwan TS, Hammill CW, Hansen PD. Laparoscopic radiofrequency ablation for the management of colorectal liver metastases: 10-year experience. J Surg Oncol. 2013;107(4):324-8.

122. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg. 2011;146(12):1416-23.

CONFIDENTIAL

123. Kingham TP, Tanoue M, Eaton A, Rocha FG, Do R, Allen P, et al. Patterns of recurrence after ablation of colorectal cancer liver metastases. Ann Surg Oncol. 2012;19(3):834-41.

124. Knudsen AR, Kannerup AS, Mortensen FV, Nielsen DT. Radiofrequency ablation of colorectal liver metastases downstaged by chemotherapy. Acta Radiol. 2009;50(7):716-21.

125. Ko S, Jo H, Yun S, Park E, Kim S, Seo HI. Comparative analysis of radiofrequency ablation and resection for resectable colorectal liver metastases. World J Gastroenterol. 2014;20(2):525-31.

126. Kornprat P, Jarnagin WR, DeMatteo RP, Fong Y, Blumgart LH, D'Angelica M. Role of intraoperative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer. Arch Surg. 2007;142(11):1087-92.

127. Kuvshinoff BW, Ota DM. Radiofrequency ablation of liver tumors: influence of technique and tumor size. Surgery. 2002;132(4):605-11; discussion 11-2.

128. Kwan BY, Kielar AZ, El-Maraghi RH, Garcia LM. Retrospective review of efficacy of radiofrequency ablation for treatment of colorectal cancer liver metastases from a Canadian perspective. Can Assoc Radiol J. 2014;65(1):77-85.

129. Lahat E, Eshkenazy R, Zendel A, Zakai BB, Maor M, Dreznik Y, et al. Complications after percutaneous ablation of liver tumors: a systematic review. Hepatobiliary Surg Nutr. 2014;3(5):317-23.

130. Lao OB, Farjah F, Flum DR, Yeung RS. Adverse events after radiofrequency ablation of unresectable liver tumors: a single-center experience. Am J Surg. 2009;198(1):76-82.

131. Lau TN, Lo RH, Tan BS. Colorectal hepatic metastases: Role of radiofrequency ablation. Ann Acad Med Singapore. 2003;32(2):212-8.

CONFIDENTIAL

132. Leblanc F, Fonck M, Brunet R, Becouarn Y, Mathoulin-Pelissier S, Evrard S. Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. Eur J Surg Oncol. 2008;34(2):185-90.

133. Lencioni R. What is the long-term survival benefit of radiofrequency ablation in patients with colorectal liver metastases? Nat Clin Pract Gastroenterol Hepatol. 2008;5(5):246-7.

134. Lencioni R, Goletti O, Armillotta N, Paolicchi A, Moretti M, Cioni D, et al. Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol. 1998;8(7):1205-11.

135. Lermite E, Lebigot J, Oberti F, Pessaux P, Aube C, Cales P, et al. Radiofrequency thermal ablation of liver carcinoma. Prospective study of 82 lesions. Gastroenterol Clin Biol. 2006;30(1):130-5.

136. Leung EY, Roxburgh CS, Leen E, Horgan PG. Combined resection and radiofrequency ablation for bilobar colorectal cancer liver metastases. Hepatogastroenterology. 2010;57(97):41-6.

137. Liang P, Dong B, Yu X, Yang Y, Yu D, Su L, et al. Prognostic factors for percutaneous microwave coagulation therapy of hepatic metastases. AJR Am J Roentgenol. 2003;181(5):1319-25.

138. Liang P, Wang Y, Yu X, Dong B. Malignant liver tumors: treatment with percutaneous microwave ablation--complications among cohort of 1136 patients. Radiology. 2009;251(3):933-40.

139. Liu CH, Arellano RS, Uppot RN, Samir AE, Gervais DA, Mueller PR. Radiofrequency ablation of hepatic tumours: effect of post-ablation margin on local tumour progression. Eur Radiol. 2010;20(4):877-85.

CONFIDENTIAL

140. Liu CH, Yu CY, Chang WC, Dai MS, Hsiao CW, Chou YC. Radiofrequency ablation of hepatic metastases: factors influencing local tumor progression. Ann Surg Oncol. 2014;21(9):3090-5.

141. Liu Y, Li S, Wan X, Li Y, Li B, Zhang Y, et al. Efficacy and safety of thermal ablation in patients with liver metastases. Eur J Gastroenterol Hepatol. 2013;25(4):442-6.

142. Livraghi T, Meloni F, Solbiati L, Zanus G, Collaborative Italian Group using As. Complications of microwave ablation for liver tumors: results of a multicenter study. Cardiovasc Intervent Radiol. 2012;35(4):868-74.

143. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer. 2003;97(12):3027-35.

144. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology. 2003;226(2):441-51.

145. Lorentzen T, Skjoldbye BO, Nolsoe CP. Microwave ablation of liver metastases guided by contrast-enhanced ultrasound: experience with 125 metastases in 39 patients. Ultraschall Med. 2011;32(5):492-6.

146. Low SC, Lo RH, Lau TN, Ooi LL, Ho CK, Tan BS, et al. Image-guided radiofrequency ablation of liver malignancies: experience at Singapore General Hospital. Ann Acad Med Singapore. 2006;35(12):851-7.

147. Lubner MG, Brace CL, Ziemlewicz TJ, Hinshaw JL, Lee FT, Jr. Microwave ablation of hepatic malignancy. Semin Intervent Radiol. 2013;30(1):56-66.

148. Machi J. Radiofrequency ablation for multiple hepatic metastases. Ann Surg Oncol. 2001;8(4):379-80.

CONFIDENTIAL

149. Machi J, Oishi AJ, Sumida K, Sakamoto K, Furumoto NL, Oishi RH, et al. Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. Cancer J. 2006;12(4):318-26.

150. Majerovic M, Augustin G, Jelincic Z, Bukovic D, Kekez T, Matosevic P, et al. Radiofrequency ablation as locoregional therapy for unresectable hepatic malignancies: initial results in 24 patients with 5-years follow-up. Coll Antropol. 2008;32(3):703-7.

151. Martin RC, Scoggins CR, McMasters KM. Microwave hepatic ablation: initial experience of safety and efficacy. J Surg Oncol. 2007;96(6):481-6.

152. Mazziotti A, Grazi GL, Gardini A, Cescon M, Pierangeli F, Ercolani G, et al. An appraisal of percutaneous treatment of liver metastases. Liver Transpl Surg. 1998;4(4):271-5.

153. McKay A, Dixon E, Taylor M. Current role of radiofrequency ablation for the treatment of colorectal liver metastases. Br J Surg. 2006;93(10):1192-201.

154. Mima K, Beppu T, Chikamoto A, Miyamoto Y, Nakagawa S, Kuroki H, et al. Hepatic resection combined with radiofrequency ablation for initially unresectable colorectal liver metastases after effective chemotherapy is a safe procedure with a low incidence of local recurrence. Int J Clin Oncol. 2013;18(5):847-55.

155. Minami Y, Kudo M. Radiofrequency ablation of liver metastases from colorectal cancer: a literature review. Gut Liver. 2013;7(1):1-6.

156. Minami Y, Kudo M, Chung H, Inoue T, Takahashi S, Hatanaka K, et al. Percutaneous radiofrequency ablation of sonographically unidentifiable liver tumors. Feasibility and usefulness of a novel guiding technique with an integrated system of computed tomography and sonographic images. Oncology. 2007;72 Suppl 1:111-6.

CONFIDENTIAL

157. Morikawa S, Inubushi T, Kurumi Y, Naka S, Sato K, Tani T, et al. MR-guided microwave thermocoagulation therapy of liver tumors: initial clinical experiences using a 0.5 T open MR system. J Magn Reson Imaging. 2002;16(5):576-83.

158. Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, et al. Complications of radiofrequency coagulation of liver tumours. Br J Surg. 2002;89(10):1206-22.

159. Mulier S, Ni Y, Jamart J, Michel L, Marchal G, Ruers T. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? Ann Surg Oncol. 2008;15(1):144-57.

160. Nagata Y, Hiraoka M, Akuta K, Abe M, Takahashi M, Jo S, et al. Radiofrequency thermotherapy for malignant liver tumors. Cancer. 1990;65(8):1730-6.

161. Nagata Y, Hiraoka M, Nishimura Y, Masunaga S, Mitumori M, Okuno Y, et al. Clinical results of radiofrequency hyperthermia for malignant liver tumors. Int J Radiat Oncol Biol Phys. 1997;38(2):359-65.

162. Navarra G, Ayav A, Weber JC, Jensen SL, Smadga C, Nicholls JP, et al. Short- and-long term results of intraoperative radiofrequency ablation of liver metastases. Int J Colorectal Dis. 2005;20(6):521-8.

163. Ng KK, Lam CM, Poon RT, Ai V, Tso WK, Fan ST. Thermal ablative therapy for malignant liver tumors: a critical appraisal. J Gastroenterol Hepatol. 2003;18(6):616-29.

164. Nielsen K, van Tilborg AA, Meijerink MR, Macintosh MO, Zonderhuis BM, de Lange ES, et al. Incidence and treatment of local site recurrences following RFA of colorectal liver metastases. World J Surg. 2013;37(6):1340-7.

165. North DA, Groeschl RT, Sindram D, Martinie JB, Iannitti DA, Bloomston M, et al. Microwave ablation for hepatic malignancies: a call for standard reporting and outcomes. Am J Surg. 2014;208(2):284-94.

CONFIDENTIAL

166. Nouso K, Kobayashi Y, Nakamura S, Uematsu S, Shiraga K, Iwadou S, et al. Application of radiofrequency ablation for the treatment of metastatic liver cancers. Hepatogastroenterology. 2010;57(97):117-20.

167. Ogata Y, Uchida S, Hisaka T, Horiuchi H, Mori S, Ishibashi N, et al. Intraoperative thermal ablation therapy for small colorectal metastases to the liver. Hepatogastroenterology. 2008;55(82-83):550-6.

168. Ong SL, Gravante G, Metcalfe MS, Strickland AD, Dennison AR, Lloyd DM. Efficacy and safety of microwave ablation for primary and secondary liver malignancies: a systematic review. Eur J Gastroenterol Hepatol. 2009;21(6):599-605.

169. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg. 2003;90(10):1240-3.

170. Oshowo A, Gillams AR, Lees WR, Taylor I. Radiofrequency ablation extends the scope of surgery in colorectal liver metastases. Eur J Surg Oncol. 2003;29(3):244-7.

171. Panpikoon T, Treesit T, Thapaneeyakorn J, Wedsart B, Inman T. Efficacy of percutaneous radiofrequency ablation of hepatic malignant tumors using a perfused-cooled electrode. J Med Assoc Thai. 2013;96(1):77-82.

172. Park MJ, Kim TH, Lee KM, Cheong JY, Kim JK. Radiofrequency ablation of metastatic liver masses: recurrence patterns and prognostic factors based on radiologic features. Hepatogastroenterology. 2013;60(123):563-7.

173. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. 2003;10(9):1059-69.

174. Pepple PT, Gerber DA. Laparoscopic-assisted ablation of hepatic tumors: a review. Semin Intervent Radiol. 2014;31(2):125-8.

CONFIDENTIAL

175. Petrovich Z, Langholz B, Astrahan M, Emami B. Deep microwave hyperthermia for metastatic tumors of the liver. Recent Results Cancer Res. 1988;107:244-8.

176. Poggi G, Riccardi A, Quaretti P, Teragni C, Delmonte A, Amatu A, et al. Complications of percutaneous radiofrequency thermal ablation of primary and secondary lesions of the liver. Anticancer Res. 2007;27(4C):2911-6.

177. Polignano FM, Quyn AJ, Sanjay P, Henderson NA, Tait IS. Totally laparoscopic strategies for the management of colorectal cancer with synchronous liver metastasis. Surg Endosc. 2012;26(9):2571-8.

178. Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST, et al. Learning curve for radiofrequency ablation of liver tumors: prospective analysis of initial 100 patients in a tertiary institution. Ann Surg. 2004;239(4):441-9.

179. Popescu I, Alexandrescu S, Croitoru A, Boros M. Strategies to convert to resectability the initially unresectable colorectal liver metastases. Hepatogastroenterology. 2009;56(91-92):739-44.

180. Poulou LS, Ziakas PD, Xila V, Vakrinos G, Malagari K, Syrigos KN, et al. Percutaneous radiofrequency ablation for unresectable colorectal liver metastases: time for shadows to disperse. Rev Recent Clin Trials. 2009;4(3):140-6.

181. Qiu J, Chen S, Wu H. Long-term outcomes after hepatic resection combined with radiofrequency ablation for initially unresectable multiple and bilobar liver malignancies. J Surg Res. 2014;188(1):14-20.

182. Rasmussen F. Radiofrequency ablation of liver metastases improves the survival rate of patients with metastatic colorectal disease. Acta Radiol. 2007;48(3):250-1.

183. Rath GK, Julka PK, Thulkar S, Sharma DN, Bahl A, Bhatnagar S. Radiofrequency ablation of hepatic metastasis: results of treatment in forty patients. J Cancer Res Ther. 2008;4(1):14-7.

CONFIDENTIAL

184. Razafindratsira T, Isambert M, Evrard S. Complications of intraoperative radiofrequency ablation of liver metastases. HPB (Oxford). 2011;13(1):15-23.

185. Reuter NP, Woodall CE, Scoggins CR, McMasters KM, Martin RC. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg. 2009;13(3):486-91.

186. Rhim H, Lim HK, Kim YS, Choi D, Lee WJ. Radiofrequency ablation of hepatic tumors: lessons learned from 3000 procedures. J Gastroenterol Hepatol. 2008;23(10):1492-500.

187. Ribeiro MA, Jr., Rodrigues JJ, Habr-Gama A, Chaib E, D'Ipolitto G, Fonseca AZ, et al. Radiofrequency ablation of primary and metastatic liver tumors--4 years experience. Hepatogastroenterology. 2007;54(76):1170-5.

188. Ritz JP, Lehmann KS, Isbert C, Reissfelder C, Albrecht T, Stein T, et al. In-vivo evaluation of a novel bipolar radiofrequency device for interstitial thermotherapy of liver tumors during normal and interrupted hepatic perfusion. J Surg Res. 2006;133(2):176-84.

189. Ritz JP, Lehmann KS, Reissfelder C, Albrecht T, Frericks B, Zurbuchen U, et al. Bipolar radiofrequency ablation of liver metastases during laparotomy. First clinical experiences with a new multipolar ablation concept. Int J Colorectal Dis. 2006;21(1):25-32.

190. Rocha FG, D'Angelica M. Treatment of liver colorectal metastases: role of laparoscopy, radiofrequency ablation, and microwave coagulation. J Surg Oncol. 2010;102(8):968-74.

191. Rose DM, Allegra DP, Bostick PJ, Foshag LJ, Bilchik AJ. Radiofrequency ablation: a novel primary and adjunctive ablative technique for hepatic malignancies. Am Surg. 1999;65(11):1009-14.

192. Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR Am J Roentgenol. 1996;167(3):759-68.

CONFIDENTIAL

193. Ruers T, Punt C, Van Coevorden F, Pierie JP, Borel-Rinkes I, Ledermann JA, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol. 2012;23(10):2619-26.

194. Ruers TJ, Joosten JJ, Wiering B, Langenhoff BS, Dekker HM, Wobbes T, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. Ann Surg Oncol. 2007;14(3):1161-9.

195. Schumacher G, Eisele R, Spinelli A, Schmidt SC, Jacob D, Pratschke J, et al. Indications for hand-assisted laparoscopic radiofrequency ablation for liver tumors. J Laparoendosc Adv Surg Tech A. 2007;17(2):153-9.

196. Scudamore CH, Lee SI, Patterson EJ, Buczkowski AK, July LV, Chung SW, et al. Radiofrequency ablation followed by resection of malignant liver tumors. Am J Surg. 1999;177(5):411-7.

197. Seidenfeld J, Korn A, Aronson N. Radiofrequency ablation of unresectable liver metastases. J Am Coll Surg. 2002;195(3):378-86.

198. Seror O, Haddar D, N'Kontchou G, Ajavon Y, Trinchet JC, Beaugrand M, et al. Radiofrequency ablation for the treatment of liver tumors in the caudate lobe. J Vasc Interv Radiol. 2005;16(7):981-90.

199. Sgouros J, Cast J, Garadi KK, Belechri M, Breen DJ, Monson JR, et al. Chemotherapy plus percutaneous radiofrequency ablation in patients with inoperable colorectal liver metastases. World J Gastrointest Oncol. 2011;3(4):60-6.

200. Shetty SK, Rosen MP, Raptopoulos V, Goldberg SN. Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms. J Vasc Interv Radiol. 2001;12(7):823-33.

CONFIDENTIAL

201. Shibata T, Murakami T, Ogata N. Percutaneous microwave coagulation therapy for patients with primary and metastatic hepatic tumors during interruption of hepatic blood flow. Cancer. 2000;88(2):302-11.

202. Shibata T, Niinobu T, Ogata N, Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer. 2000;89(2):276-84.

203. Shimada S, Hirota M, Beppu T, Matsuda T, Hayashi N, Tashima S, et al. Complications and management of microwave coagulation therapy for primary and metastatic liver tumors. Surg Today. 1998;28(11):1130-7.

204. Shukla PJ, Barreto SG. Surgery for malignant liver tumors. J Cancer Res Ther. 2009;5(3):154-60.

205. Siperstein A, Garland A, Engle K, Rogers S, Berber E, Foroutani A, et al. Local recurrence after laparoscopic radiofrequency thermal ablation of hepatic tumors. Ann Surg Oncol. 2000;7(2):106-13.

206. Siperstein A, Garland A, Engle K, Rogers S, Berber E, String A, et al. Laparoscopic radiofrequency ablation of primary and metastatic liver tumors. Technical considerations. Surg Endosc. 2000;14(4):400-5.

207. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg. 2007;246(4):559-65; discussion 65-7.

208. Snoeren N, Nijkamp MW, Berendsen T, Govaert KM, van Kessel CS, Borel Rinkes IH, et al. Multipolar radiofrequency ablation for colorectal liver metastases close to major hepatic vessels. Surgeon. 2015;13(2):77-82.

209. Sofocleous CT, Petre EN, Gonen M, Brown KT, Solomon SB, Covey AM, et al. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. J Vasc Interv Radiol. 2011;22(6):755-61.

CONFIDENTIAL

210. Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology. 2012;265(3):958-68.

211. Solbiati L, Goldberg SN, Ierace T, Livraghi T, Meloni F, Dellanoce M, et al. Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrodes. Radiology. 1997;205(2):367-73.

212. Solbiati L, Livraghi T, Goldberg SN, Ierace T, Meloni F, Dellanoce M, et al. Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology. 2001;221(1):159-66.

213. Sorensen SM, Mortensen FV, Nielsen DT. Radiofrequency ablation of colorectal liver metastases: long-term survival. Acta Radiol. 2007;48(3):253-8.

214. Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009;45(10):1748-56.

215. Stang A, Oldhafer KJ, Weilert H, Keles H, Donati M. Selection criteria for radiofrequency ablation for colorectal liver metastases in the era of effective systemic therapy: a clinical score based proposal. BMC Cancer. 2014;14:500.

216. Stattner S, Jones RP, Yip VS, Buchanan K, Poston GJ, Malik HZ, et al. Microwave ablation with or without resection for colorectal liver metastases. Eur J Surg Oncol. 2013;39(8):844-9.

217. Stattner S, Primavesi F, Yip VS, Jones RP, Ofner D, Malik HZ, et al. Evolution of surgical microwave ablation for the treatment of colorectal cancer liver metastasis: review of the literature and a single centre experience. Surg Today. 2015;45(4):407-15.

218. Stintzing S, Grothe A, Hendrich S, Hoffmann RT, Heinemann V, Rentsch M, et al. Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. Acta Oncol. 2013;52(5):971-7.

CONFIDENTIAL

219. Sun W. Advanced local therapies for the treatment of limited systemic mCRC. Oncology (Williston Park). 2014;28(11):1006-7.

220. Suppiah A, White TJ, Roy-Choudhury SH, Breen DJ, Cast J, Maraveyas A, et al. Long-term results of percutaneous radiofrequency ablation of unresectable colorectal hepatic metastases: final outcomes. Dig Surg. 2007;24(5):358-60.

221. Takaki H, Yamakado K, Nakatsuka A, Yamada T, Shiraki K, Takei Y, et al. Frequency of and risk factors for complications after liver radiofrequency ablation under CT fluoroscopic guidance in 1500 sessions: single-center experience. AJR Am J Roentgenol. 2013;200(3):658-64.

222. Tanis E, Nordlinger B, Mauer M, Sorbye H, van Coevorden F, Gruenberger T, et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer. 2014;50(5):912-9.

223. Tepel J, Hinz S, Klomp HJ, Kapischke M, Kremer B. Intraoperative radiofrequency ablation (RFA) for irresectable liver malignancies. Eur J Surg Oncol. 2004;30(5):551-5.

224. Topal B, Hompes D, Aerts R, Fieuws S, Thijs M, Penninckx F. Morbidity and mortality of laparoscopic vs. open radiofrequency ablation for hepatic malignancies. Eur J Surg Oncol. 2007;33(5):603-7.

225. Tropea A, Biondi A, Corsaro A, Donati M, Basile F, Gruttadauria S. Combined microwave thermal ablation and liver resection for single step treatment of otherwise unresectable colorectal liver metastases; a monoistitutional experiences. Eur Rev Med Pharmacol Sci. 2014;18(2 Suppl):6-10.

226. Tsai S, Pawlik TM. Outcomes of ablation versus resection for colorectal liver metastases: are we comparing apples with oranges? Ann Surg Oncol. 2009;16(9):2422-8.

CONFIDENTIAL

227. Ungureanu BS, Sandulescu L, Surlin V, Sparchez Z, Saftoiu A. Surgical hepatic resection vs. ultrasonographic guided radiofrequency ablation in colorectal liver metastases: what should we choose? Med Ultrason. 2014;16(2):145-51.

228. Van den Eynde M, Hendlisz A. Treatment of colorectal liver metastases: a review. Rev Recent Clin Trials. 2009;4(1):56-62.

229. Van Tilborg AA, Meijerink MR, Sietses C, Van Waesberghe JH, Mackintosh MO, Meijer S, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. Br J Radiol. 2011;84(1002):556-65.

230. Veltri A, Gazzera C, Rotondella C, Camerano F, Busso M, Gandini G. Image-guided microwave ablation of hepatic tumours: preliminary experience. Radiol Med. 2012;117(3):378-92.

231. Veltri A, Guarnieri T, Gazzera C, Busso M, Solitro F, Fora G, et al. Long-term outcome of radiofrequency thermal ablation (RFA) of liver metastases from colorectal cancer (CRC): size as the leading prognostic factor for survival. Radiol Med. 2012;117(7):1139-51.

232. Veltri A, Sacchetto P, Tosetti I, Pagano E, Fava C, Gandini G. Radiofrequency ablation of colorectal liver metastases: small size favorably predicts technique effectiveness and survival. Cardiovasc Intervent Radiol. 2008;31(5):948-56.

233. Vlad L, Osian G, Branda H, Sparchez Z, Miclaus D, Furcea L, et al. Radiofrequency by open surgical approach in the treatment of hepatic tumours: early experience with 14 cases. Rom J Gastroenterol. 2003;12(2):113-8.

234. Vogl TJ, Dommermuth A, Heinle B, Nour-Eldin NE, Lehnert T, Eichler K, et al. Colorectal cancer liver metastases: long-term survival and progression-free survival after thermal ablation using magnetic resonance-guided laser-induced interstitial thermotherapy in 594 patients: analysis of prognostic factors. Invest Radiol. 2014;49(1):48-56.

CONFIDENTIAL

235. Vogl TJ, Farshid P, Naguib NN, Darvishi A, Bazrafshan B, Mbalisike E, et al. Thermal ablation of liver metastases from colorectal cancer: radiofrequency, microwave and laser ablation therapies. Radiol Med. 2014;119(7):451-61.

236. von Breitenbuch P, Kohl G, Guba M, Geissler E, Jauch KW, Steinbauer M. Thermoablation of colorectal liver metastases promotes proliferation of residual intrahepatic neoplastic cells. Surgery. 2005;138(5):882-7.

237. Wang X, Sofocleous CT, Erinjeri JP, Petre EN, Gonen M, Do KG, et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Cardiovasc Intervent Radiol. 2013;36(1):166-75.

238. Weng M, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One. 2012;7(9):e45493.

239. Wertenbroek MW, Schepers M, Kamminga-Rasker HJ, Bottema JT, Muller Kobold AC, Roelofsen H, et al. Clinical outcome, proteome kinetics and angiogenic factors in serum after thermoablation of colorectal liver metastases. BMC Cancer. 2013;13:266.

240. White RR, Avital I, Sofocleous CT, Brown KT, Brody LA, Covey A, et al. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg. 2007;11(3):256-63.

241. Wong J, Lee KF, Lee PS, Ho SS, Yu SC, Ng WW, et al. Radiofrequency ablation for 110 malignant liver tumours: preliminary results on percutaneous and surgical approaches. Asian J Surg. 2009;32(1):13-20.

242. Wong J, Lee KF, Yu SC, Lee PS, Cheung YS, Chong CN, et al. Percutaneous radiofrequency ablation versus surgical radiofrequency ablation for malignant liver tumours: the long-term results. HPB (Oxford). 2013;15(8):595-601.

243. Wong SL, Edwards MJ, Chao C, Simpson D, McMasters KM. Radiofrequency ablation for unresectable hepatic tumors. Am J Surg. 2001;182(6):552-7.

CONFIDENTIAL

244. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD, 3rd, Dorfman GS, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493-508.

245. Wood TF, Rose DM, Chung M, Allegra DP, Foshag LJ, Bilchik AJ. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. Ann Surg Oncol. 2000;7(8):593-600.

246. Wu YZ, Li B, Wang T, Wang SJ, Zhou YM. Radiofrequency ablation vs hepatic resection for solitary colorectal liver metastasis: a meta-analysis. World J Gastroenterol. 2011;17(36):4143-8.

247. Yang S, Alibhai SM, Kennedy ED, El-Sedfy A, Dixon M, Coburn N, et al. Optimal management of colorectal liver metastases in older patients: a decision analysis. HPB (Oxford). 2014;16(11):1031-42.

248. Zagoria RJ, Chen MY, Shen P, Levine EA. Complications from radiofrequency ablation of liver metastases. Am Surg. 2002;68(2):204-9.

249. Zdenkowski N, Chen S, van der Westhuizen A, Ackland S. Curative strategies for liver metastases from colorectal cancer: a review. Oncologist. 2012;17(2):201-11.

250. Zhang X, Chen B, Hu S, Wang L, Wang K, Wachtel MS, et al. Microwave ablation with cooled-tip electrode for liver cancer: an analysis of 160 cases. Hepatogastroenterology. 2008;55(88):2184-7.

251. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg. 2006;141(5):460-6; discussion 6-7.

252. Ruers T, Punt CJA, van Coevorden F, Pierie J-P, Borel Rinkes I, Ledermann JA, et al. Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC). ASCO Meeting Abstracts. 2015;33(15_suppl):3501.

CONFIDENTIAL

253. Marijnen. Colorectaalcarcinoom Landelijke richtlijn, Versie 3.0 2014 [Available from: http://www.oncoline.nl/colorectaalcarcinoom.

254. Scorsetti M, Comito T, Tozzi A, Navarria P, Fogliata A, Clerici E, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141(3):543-53.

255. Petrelli F, Comito T, Barni S, Pancera G, Scorsetti M, Ghidini A, et al. Stereotactic body radiotherapy for colorectal cancer liver metastases: A systematic review. Radiother Oncol. 2018.

256. McPartlin A, Swaminath A, Wang R, Pintilie M, Brierley J, Kim J, et al. Long-Term Outcomes of Phase 1 and 2 Studies of SBRT for Hepatic Colorectal Metastases. Int J Radiat Oncol Biol Phys. 2017;99(2):388-95.

257. Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol. 2009;27(10):1572-8.

258. Mahadevan A, Blanck O, Lanciano R, Peddada A, Sundararaman S, D'Ambrosio D, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch(R) Patient Registry. Radiat Oncol. 2018;13(1):26.

259. Andratschke N, Alheid H, Allgauer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer. 2018;18(1):283.

260. Lee MT, Kim JJ, Dinniwell R, Brierley J, Lockwood G, Wong R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol. 2009;27(10):1585-91.

CONFIDENTIAL

261. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005;25 Suppl 1:S69-83.

262. Lencioni R, de Baere T, Martin RC, Nutting CW, Narayanan G. Image-Guided Ablation of Malignant Liver Tumors: Recommendations for Clinical Validation of Novel Thermal and Non-Thermal Technologies - A Western Perspective. Liver Cancer. 2015;4(4):208-14.

263. Tanaka K, Shimada H, Nagano Y, Endo I, Sekido H, Togo S. Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver. Surgery. 2006;139(2):263-73.

264. Leung U, Kuk D, D'Angelica MI, Kingham TP, Allen PJ, DeMatteo RP, et al. Long-term outcomes following microwave ablation for liver malignancies. Br J Surg. 2015;102(1):85-91.

265. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol. 2010;17(1):171-8.

266. Correa-Gallego C, Fong Y, Gonen M, D'Angelica MI, Allen PJ, DeMatteo RP, et al. A retrospective comparison of microwave ablation vs. radiofrequency ablation for colorectal cancer hepatic metastases. Ann Surg Oncol. 2014;21(13):4278-83.

267. Eng OS, Tsang AT, Moore D, Chen C, Narayanan S, Gannon CJ, et al. Outcomes of microwave ablation for colorectal cancer liver metastases: a single center experience. J Surg Oncol. 2015;111(4):410-3.

268. Groeschl RT, Wong RK, Quebbeman EJ, Tsai S, Turaga KK, Pappas SG, et al. Recurrence after microwave ablation of liver malignancies: a single institution experience. HPB (Oxford). 2013;15(5):365-71.

269. Liang PC, Lai HS, Shih TT, Wu CH, Huang KW. The pilot experience upon surgical ablation of large liver tumor by microwave system with tissue permittivity feedback control mechanism. BMC Surg. 2014;14:82.

CONFIDENTIAL

270. Groeschl RT, Pilgrim CH, Hanna EM, Simo KA, Swan RZ, Sindram D, et al. Microwave ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg. 2014;259(6):1195-200.

271. Seki T, Wakabayashi M, Nakagawa T, Imamura M, Tamai T, Nishimura A, et al. Percutaneous microwave coagulation therapy for solitary metastatic liver tumors from colorectal cancer: a pilot clinical study. Am J Gastroenterol. 1999;94(2):322-7.

272. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg. 2005;242(2):158-71.

273. Takahashi H, Kahramangil B, Berber E. Local recurrence after microwave thermosphere ablation of malignant liver tumors: results of a surgical series. Surgery. 2018;163(4):709-13.

274. Engstrand J, Nilsson H, Jansson A, Isaksson B, Freedman J, Lundell L, et al. A multiple microwave ablation strategy in patients with initially unresectable colorectal cancer liver metastases - A safety and feasibility study of a new concept. Eur J Surg Oncol. 2014;40(11):1488-93.

275. Wang J, Liang P, Yu J, Yu MA, Liu F, Cheng Z, et al. Clinical outcome of ultrasound-guided percutaneous microwave ablation on colorectal liver metastases. Oncol Lett. 2014;8(1):323-6.

276. Comito T, Clerici E, Tozzi A, D'Agostino G. Liver metastases and SBRT: A new paradigm? Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology. 2015;20(6):464-71.

277. Dawson LA, Normolle D, Balter JM, McGinn CJ, Lawrence TS, Ten Haken RK. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys. 2002;53(4):810-21.

278. Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother Oncol. 2008;86(1):25-9.

CONFIDENTIAL

279. Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. Semin Radiat Oncol. 2014;24(3):196-9.

280. Marijnen CAM. Colorectaalcarcinoom Landelijke richtlijn, Versie: 3.0: Intergraal Kankercentrum Nederland (IKNL); 2014 [updated 16-04-2016. Available from: http://www.oncoline.nl/colorectaalcarcinoom.

281. Mendez Romero A, de Man RA. Stereotactic body radiation therapy for primary and metastatic liver tumors: From technological evolution to improved patient care. Best Pract Res Clin Gastroenterol. 2016;30(4):603-16.

282. Aitken KL, Tait DM, Nutting CM, Khabra K, Hawkins MA. Risk-adapted strategy partial liver irradiation for the treatment of large volume metastatic liver disease. Acta Oncol. 2014;53(5):702-6.

283. Ambrosino G, Polistina F, Costantin G, Francescon P, Guglielmi R, Zanco P, et al. Image-guided robotic stereotactic radiosurgery for unresectable liver metastases: preliminary results. Anticancer Res. 2009;29(8):3381-4.

284. Goodman KA, Wiegner EA, Maturen KE, Zhang Z, Mo Q, Yang G, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys. 2010;78(2):486-93.

285. Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol. 2006;45(7):823-30.

286. Katz AW, Carey-Sampson M, Muhs AG, Milano MT, Schell MC, Okunieff P. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys. 2007;67(3):793-8.

CONFIDENTIAL

287. Scorsetti M, Arcangeli S, Tozzi A, Comito T, Alongi F, Navarria P, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys. 2013;86(2):336-42.

288. van der Pool AE, Mendez Romero A, Wunderink W, Heijmen BJ, Levendag PC, Verhoef C, et al. Stereotactic body radiation therapy for colorectal liver metastases. Br J Surg. 2010;97(3):377-82.

289. Wada H, Takai Y, Nemoto K, Yamada S. Univariate analysis of factors correlated with tumor control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumors. Int J Radiat Oncol Biol Phys. 2004;58(4):1114-20.

290. Wulf J, Guckenberger M, Haedinger U, Oppitz U, Mueller G, Baier K, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. Acta Oncol. 2006;45(7):838-47.

291. Yamashita H, Onishi H, Matsumoto Y, Murakami N, Matsuo Y, Nomiya T, et al. Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. Radiat Oncol. 2014;9:112.

292. Yuan ZY, Meng MB, Liu CL, Wang HH, Jiang C, Song YC, et al. Stereotactic body radiation therapy using the CyberKnife((R)) system for patients with liver metastases. Onco Targets Ther. 2014;7:915-23.

293. Mendez Romero A, Wunderink W, Hussain SM, De Pooter JA, Heijmen BJ, Nowak PC, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. Acta Oncol. 2006;45(7):831-7.

294. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg. 2008;247(1):125-35.

CONFIDENTIAL

295. Minagawa M, Yamamoto J, Kosuge T, Matsuyama Y, Miyagawa S, Makuuchi M. Simplified staging system for predicting the prognosis of patients with resectable liver metastasis: development and validation. Arch Surg. 2007;142(3):269-76; discussion 77.

296. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996;77(7):1254-62.

297. Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg. 1999;189(3):291-9.

298. Nagashima I, Takada T, Matsuda K, Adachi M, Nagawa H, Muto T, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. J Hepatobiliary Pancreat Surg. 2004;11(2):79-83.

299. Konopke R, Kersting S, Distler M, Dietrich J, Gastmeier J, Heller A, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int. 2009;29(1):89-102.

300. Schindl M, Wigmore SJ, Currie EJ, Laengle F, Garden OJ. Prognostic scoring in colorectal cancer liver metastases: development and validation. Arch Surg. 2005;140(2):183-9.

301. Lise M, Bacchetti S, Da Pian P, Nitti D, Pilati P. Patterns of recurrence after resection of colorectal liver metastases: prediction by models of outcome analysis. World J Surg. 2001;25(5):638-44.

302. Ueno H, Mochizuki H, Hatsuse K, Hase K, Yamamoto T. Indicators for treatment strategies of colorectal liver metastases. Ann Surg. 2000;231(1):59-66.

CONFIDENTIAL

303. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309-18; discussion 18-21.

304. Mala T, Bohler G, Mathisen O, Bergan A, Soreide O. Hepatic resection for colorectal metastases: can preoperative scoring predict patient outcome? World J Surg. 2002;26(11):1348-53.

305. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575-80.

306. Parks R, Gonen M, Kemeny N, Jarnagin W, D'Angelica M, DeMatteo R, et al. Adjuvant chemotherapy improves survival after resection of hepatic colorectal metastases: analysis of data from two continents. J Am Coll Surg. 2007;204(5):753-61; discussion 61-3.

307. Boutros C, Somasundar P, Garrean S, Saied A, Espat NJ. Microwave coagulation therapy for hepatic tumors: review of the literature and critical analysis. Surg Oncol. 2010;19(1):e22-32.

308. Ayez N, Grunhagen DJ, De Jonge J, Ijzermans JN, Eggermont AM, Verhoef C. The Role of Neoadjuvant Chemotherapy in Patients with Resectable Colorectal Liver Metastases. Annals of Surgical Oncology. 2012;19:S35-S.

309. Rahbari NN, Reissfelder C, Schulze-Bergkamen H, Jager D, Buchler MW, Weitz J, et al. Adjuvant therapy after resection of colorectal liver metastases: the predictive value of the MSKCC clinical risk score in the era of modern chemotherapy. BMC Cancer. 2014;14:174.

310. Comprehensive Cancer Organisation the Netherlands (I.K.N.L.). National evidence-based guideline. Colorectaalcarcinoom. Available from: http://oncolinenl/. 2014.

311. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006;243(1):1-7.

CONFIDENTIAL

312. Kishi Y, Zorzi D, Contreras CM, Maru DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol. 2010;17(11):2870-6.

313. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006;24(13):2065-72.

314. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg. 2007;94(3):274-86.

315. Chua TC, Saxena A, Liauw W, Chu F, Morris DL. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases--a systematic review. Eur J Cancer. 2012;48(12):1757-65.

316. Byam J, Reuter NP, Woodall CE, Scoggins CR, McMasters KM, Martin RC. Should hepatic metastatic colorectal cancer patients with extrahepatic disease undergo liver resection/ablation? Ann Surg Oncol. 2009;16(11):3064-9.

317. Fiorentino F, Hunt I, Teoh K, Treasure T, Utley M. Pulmonary metastasectomy in colorectal cancer: a systematic review and quantitative synthesis. J R Soc Med. 2010;103(2):60-6.

318. Treasure T. Pulmonary metastasectomy for colorectal cancer: weak evidence and no randomised trials. Eur J Cardiothorac Surg. 2008;33(2):300-2.

319. Treasure T. Pulmonary Metastasectomy for Colorectal Cancer: Recent Reports Prompt a Review of the Available Evidence. Curr Colorectal Cancer Rep. 2014;10(3):296-302.

320. Treasure T, Fallowfield L, Farewell V, Ferry D, Lees B, Leonard P, et al. Pulmonary metastasectomy in colorectal cancer: time for a trial. Eur J Surg Oncol. 2009;35(7):686-9.

CONFIDENTIAL

321. Treasure T, Fallowfield L, Lees B, Farewell V. Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. Thorax. 2012;67(2):185-7.

322. Treasure T, Macbeth F. Percutaneous Image Guided Thermal Ablation (IGTA) therapies are to be included in the interventional arm of the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial to test if survival and quality of life are better than with intention to treat without intervention. Eur J Surg Oncol. 2016;42(3):435-6.

323. Treasure T, Russell C, Macbeth F. Re-launch of PulMiCC trial to discover the true effect of pulmonary metastasectomy on survival in advanced colorectal cancer. BMJ. 2015;351:h6045.

324. Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gonen M, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol. 2009;16(8):2138-46.

325. de Haas RJ, Wicherts DA, Adam R. Resection of colorectal liver metastases with extrahepatic disease. Dig Surg. 2008;25(6):461-6.

326. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg. 2007;84(1):324-38.

327. Pfannschmidt J, Hoffmann H, Dienemann H. Reported outcome factors for pulmonary resection in metastatic colorectal cancer. J Thorac Oncol. 2010;5(6 Suppl 2):S172-8.

328. Vidarsdottir H, Moller PH, Jonasson JG, Pfannschmidt J, Gudbjartsson T. Indications and surgical outcome following pulmonary metastasectomy: a nationwide study. Thorac Cardiovasc Surg. 2012;60(6):383-9.

329. Gootjes EC, Buffart TE, Tol MP, Burger J, Grunhagen DJ, van der Stok EP, et al. The ORCHESTRA trial: A phase III trial of adding tumor debulking to systemic therapy versus systemic therapy alone in (mCRC) multi-organ metastatic colorectal cancer. Journal of Clinical Oncology. 2015;33(15).

CONFIDENTIAL

330. Eltawil KM, Boame N, Mimeault R, Shabana W, Balaa FK, Jonker DJ, et al. Patterns of recurrence following selective intraoperative radiofrequency ablation as an adjunct to hepatic resection for colorectal liver metastases. J Surg Oncol. 2014;110(6):734-8.

331. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

332. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50 Suppl 1:122S-50S.

333. Nordholm-Carstensen A, Wille-Jorgensen PA, Jorgensen LN, Harling H. Indeterminate pulmonary nodules at colorectal cancer staging: a systematic review of predictive parameters for malignancy. Ann Surg Oncol. 2013;20(12):4022-30.

334. De Wever W, Meylaerts L, De Ceuninck L, Stroobants S, Verschakelen JA. Additional value of integrated PET-CT in the detection and characterization of lung metastases: correlation with CT alone and PET alone. Eur Radiol. 2007;17(2):467-73.

335. Parnaby CN, Bailey W, Balasingam A, Beckert L, Eglinton T, Fife J, et al. Pulmonary staging in colorectal cancer: a review. Colorectal Dis. 2012;14(6):660-70.

336. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

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Appendix 1 VAS-score, pain medication and registration form (Dutch)

Figure 1: VAS-score

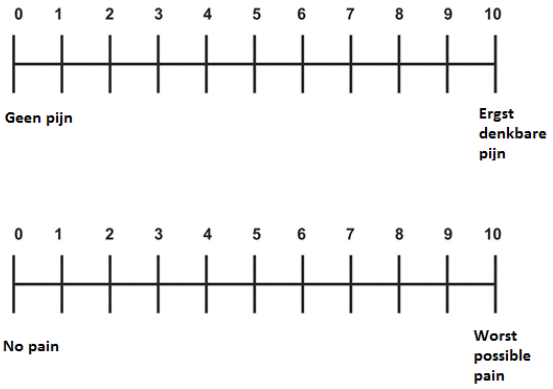
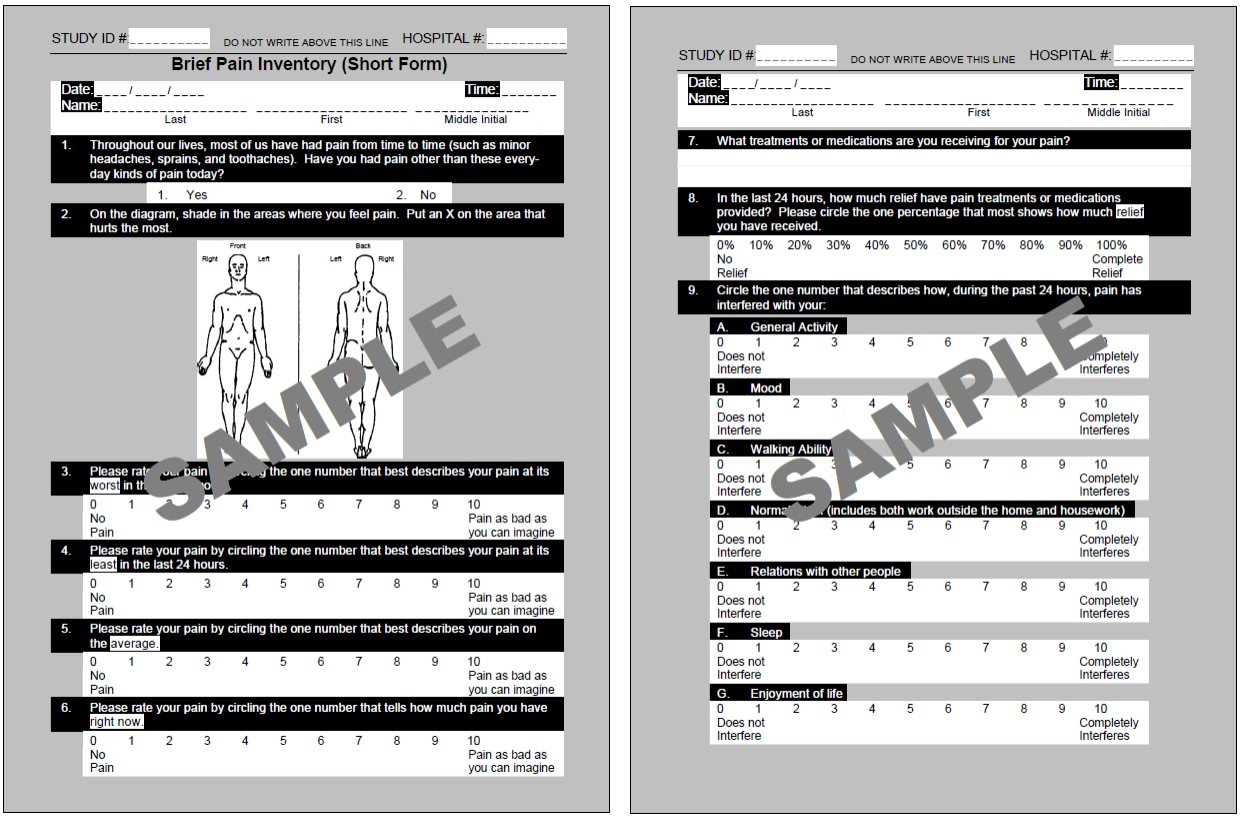


Figure 2: Pain medication and registration form


STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

Front Back

Right Left Left Right

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

SAMPLE

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No Relief — Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not Interfere — Completely Interferes

SAMPLE

Appendix 2 Questionnaires

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊⌊⌊⌊

Your birthdate (Day, Month, Year): ⌊⌊ ⌊⌊⌊ ⌊⌊

Today's date (Day, Month, Year): 31 ⌊⌊ ⌊⌊⌊ ⌊⌊

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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Specimen
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EQ - 5D

Gezondheidsvragenlijst

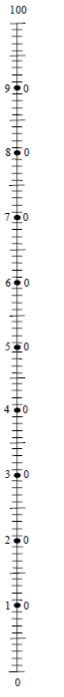
(Nederlandse versie)
(Dutch version)

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag

Best voorstelbare gezondheidstoestand



Slechtst voorstelbare gezondheidstoestand

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje achter de zin die het best past bij uw eigen gezondheidstoestand vandaag.

Mobiliteit
- Ik heb geen problemen met lopen ❑
- Ik heb enige problemen met lopen ❑
- Ik ben bedlegerig ❑

Zelfzorg
- Ik heb geen problemen om mijzelf te wassen of aan te kleden ❑
- Ik heb enige problemen om mijzelf te wassen of aan te kleden ❑
- Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*
- Ik heb geen problemen met mijn dagelijkse activiteiten ❑
- Ik heb enige problemen met mijn dagelijkse activiteiten ❑
- Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten
- Ik heb geen pijn of andere klachten ❑
- Ik heb matige pijn of andere klachten ❑
- Ik heb zeer ernstige pijn of andere klachten ❑

Stemming
- Ik ben niet angstig of somber ❑
- Ik ben matig angstig of somber ❑
- Ik ben erg angstig of somber ❑

Gezien alle antwoorden anoniem zijn, zou het ons helpen uw antwoorden beter te kunnen begrijpen indien we van iedereen wat achtergrondinformatie hebben. Mogen we u daarom vragen de volgende vragen te beantwoorden?

1. Heeft u ooit te maken gehad met een ernstige ziekte?

	Ja	Nee	
bij uzelf	❑	❑	KRUIS DE HOKJES AAN DIE VAN TOEPASSING ZIJN
bij familieleden	❑	❑	
doordat u anderen verzorgde	❑	❑	

2. Hoe oud bent u? ☐ jaar

	man	vrouw	
3. Bent u:	❑	❑	KRUIS HET HOKJE AAN DAT VAN TOEPASSING IS

4. Bent u: KRUIS HET HOKJE AAN DAT VAN TOEPASSING IS
- *roker* ❑
- *ex-roker* ❑
- *niet-roker* ❑

	Ja	Nee	
5. Werkt u nu, of heeft u ooit gewerkt, in de gezondheidszorg of de maatschappelijke dienstverlening?	❑	❑	KRUIS HET HOKJE AAN DAT VAN TOEPASSING IS

Zo ja, wat is/was uw functie? .....

6. Welke van de volgende omschrijvingen geeft uw **belangrijkste** dagelijkse werksituatie het beste weer? KRUIS HET HOKJE AAN DAT VAN TOEPASSING IS
- *betaalde baan of zelfstandig ondernemer* ❑
- *gepensioneerd* ❑
- *huishoudelijk werk* ❑
- *student* ❑
- *vrijwilligerswerk* ❑
- *(langdurig) arbeidsongeschikt* ❑
- *werkloos* ❑

7. Welke van de volgende opleidingen heeft u voltooid? KRUIS HET HOKJE AAN DAT VAN TOEPASSING IS
- *geen* ❑
- *lagere school* ❑
- *lager beroepsonderwijs (b.v. huishoudschool, LTS, LEAO)* ❑
- *middelbaar algemeen voortgezet onderwijs (b.v. MAVO, IVO, (M)ULO)* ❑
- *middelbare beroepsopleiding (b.v. MTS, MEAO, MHNO, INAS)* ❑
- *hoger algemeen en voorbereidend wetenschappelijk onderwijs (HAVO, VWO, HBS, MMS, Gymnasium, Atheneum)* ❑
- *hoger beroepsonderwijs* ❑
- *universiteit* ❑

8. Als u uw postcode weet, kunt u deze dan hier invullen: ☐

4

COLLISION XL
Colorectal Liver Metastases:
microwave ablation o rwelectric body radiotherapy

PRODISQ

VUmc VU University Medical Center Amsterdam

PATIENTNUMMER:

Vragenlijst werk, verzuim en productieverliezen

A. Betaald werk
Onder "betaald werk" wordt zowel loondienst, zelfstandig ondernemerschap, als freelance werk verstaan.

A1.	Heeft u momenteel betaald werk? ☐ Nee (ga door naar D) ☐ Ja
A2.	Voor hoeveel uur per week heeft u de aanstelling? . . . . . uren per week
A3.	Over hoeveel dagen zijn deze uren verdeeld? . . . . . dagen

B. Ziekteverzuim

B1.	Heeft u in de **afgelopen 12 maanden** een aaneengesloten periode van **5 of meer maanden** verzuimd? ☐ Nee ☐ Ja, te weten . . . . . (aantal) maanden
B2.	Heeft u in de **afgelopen 4 weken** verzuimd? ☐ Nee (ga door naar C) ☐ Ja, te weten . . . . . (aantal) **werk**dagen
B3.	Verzuimt u momenteel van uw werk? ☐ Nee ☐ Ja

C. Productieverliezen tijdens werk

C1.	Ging u in de **afgelopen 4 weken** naar uw werk terwijl u zich niet goed voelde? ☐ Nee ☐ Ja, te weten . . . . . (aantal) **werk**dagen
C2.	Op de schaal hieronder kunt u **omcirkelen** hoeveel werk u hebt gedaan tijdens een werkdag dat u zich niet goed voelde ten opzichte van een dag wanneer u zich wel goed voelt. 0 betekent "Helemaal niets gedaan" 10 betekent "Even veel gedaan als op een dag dat ik me goed voel" 0 1 2 3 4 5 6 7 8 9 10

PRODISQ

D. Productieverliezen in de huishoudelijke sfeer

D1.	Hoeveel uren per week besteedt u thuis aan het huishouden? . . . . . uren per week
D2.	Over hoeveel dagen zijn deze uren verdeeld? . . . . . dagen
D3.	Waren er in de **afgelopen 4 weken** dagen dat u thuis helemaal niet aan het huishouden kon beginnen om dat u zich niet goed voelde? ☐ Nee ☐ Ja, te weten . . . . . (aantal) dagen
D4.	Deed u in de **afgelopen 4 weken** thuis huishoudelijk werk, terwijl u zich niet goed voelde? ☐ Nee ☐ Ja, te weten . . . . . (aantal) dagen
D5.	Op de schaal hieronder kunt u **omcirkelen** hoeveel huishoudelijk werk u thuis hebt gedaan tijdens een dag dat u zich niet goed voelde ten opzichte van een dag dat u zich wel goed voelt. 0 betekent "Helemaal niets gedaan" 10 betekent "Even veel gedaan als op een dag dat ik me goed voel" 0 1 2 3 4 5 6 7 8 9 10
D6.	Heeft u in de **afgelopen 4 weken** extra huishoudelijke hulp moeten inschakelen? ☐ Nee ☐ Ja, te weten . . . . . (aantal) uur/week

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