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Real-world data of microwave ablation in colorectal liver metastases: patients, tumour characteristics and safety

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Dedicated to:

Frederika, Franziska, Daniela and my parents.

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5-FU	Fluorouracil
ADL	Age-appropriate instrumental ADL
AE	Adverse Events
AJCC	American Joint Committee on Cancer
ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
AmCORE	Amsterdam Colorectal Liver Met Registry
aNSCLC	Non-small cell lung cancer
ASA	American Society of Anaesthesiology
BRAF	V-raf murine sarcoma viral oncogene homolog B
CAPOX	Capecitabine + Oxaliplatin
CC	Colon cancer
CCC	Cholangiocellular carcinoma
CEA	Carcinoembryonales Antigen
CIEMAR	CIRSE Registry for Emprint Microwave Ablation
CIREL	CIrse Registry for LifePearl™ microspheres
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
CLM	colorectal liver metastasis
CRC	Colorectal cancer
CRLM	Colorectal liver metastasis
CT	Computed tomography
cTACE	Conventional TACE
CTCAE	Common Terminology Criteria for Adverse Events
DEB	Drug-eluting beads
DPFS	Distant progression-free survival
DSM	Degradable starch microspheres
e-OSH	Enhanced one-stage hepatectomy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FAP	Familial adenomatous polyposis
FOLFIRI	Folinic acid + 5-FU + irinotecan
FOLFOX	Folinic acid + 5-FU + oxaliplatin
GCP	Google Cloud Platform
HCC	Hepatocellular carcinoma
HDI	Human Development Index
HIFU	High-Intensity Focused Ultrasound
HRQOL	Health-related quality of life score
IR	Interventional radiology
IRE	Irreversible electroporation

KRAS	Kirsten rat sarcoma virus
LABA	Long-acting beta 2-agonist
LC	Local control
LITT	Laser interstitial tumour therapy
LP-IRI	LifePearl-irinotecan
LTPFS	Local tumour progression-free survival
LTRA	Leukotriene-receptor antagonist
M	Metastasis
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MWA	Microwave ablation
N	Nodal status
PAS	Post-ablation syndrome
PET	Positron emission tomography
PI	Principal Investigator
PLLA	Ho-poly-L-lactic acid
PS	Performance score
QoL	Quality of life
RAS	Rat sarcoma viral oncogene homolog
RC	Rectal cancer
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria In Solid Tumors
RF	Radiofrequency ablation
RS	RawScore
RWD	Real-world data
SBRT	Stereotactic body radiation therapy
SMWA	Stereotactic MWA
T	Primary tumour staging
TACE	Transarterial Chemoembolisation
TARE	Transarterial Radioembolisation
UICC	Union International Cancer Control
US	Ultrasound
VEGF	Anti-vascular endothelial growth factor

1. Introduction

1.1 Incidence and Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) is the third most diagnosed malignant disease and the fourth major cause of cancer-related deaths in the world, with almost 900 000 deaths per year, expected to enlarge by 60% by 2023, bringing approximately 2,2 million new cases and 1,1 million disease-related deaths (Buccafusca *et al.*, 2019). More than two-thirds of all CRC cases and 60% of all CRC-related deaths are present in countries with a high human development index (HDI) (Ferlay *et al.*, 2015). In many medium-to-high HDI countries, especially in Asia, Eastern Europe, and South America, an increase in CRC incidence and mortality is now monitored, contrary to declining or stabilising numbers in the highest-indexed HDI countries in the world (Center *et al.*, 2009). The declining rates in incidence in the highest indexed HDI countries are attributed to prevention and nationwide screening programs, namely with the increased use of coloscopy, as well as improvements in oncological and surgical therapies contributing to declining mortality rates.

CRC is the second most diagnosed cancer disease in women and third most in men; the incidence and mortality rates in women are 25% lower than in men.

1.2 Etiology of CRC

As a risk of becoming CRC, both hereditary and environmental factors are crucial. Positive family history seems to play a vital role in approximately 10-20% of all patients with diagnosed CRC, with a differing risk determined by the degree and number of affected relatives and age of the primary diagnosis of CRC (Henrikson *et al.*, 2015; Schoen *et al.*, 2015). Some cancer susceptibility genes (single-nucleotide polymorphism) that are identified with CRC risk were pointed out in a

few genome-wide studies of CRC. However, still, most hereditary factors that are associated with CRC risk are still subject to further research (Jiao *et al.*, 2014).

5 – 7% of the patients affected with CRC are monitored as a subgroup with well-determined hereditary CRC syndromes (Syngal *et al.*, 2015).
Hereditary CRC-Syndromes can be divided into polyposis syndromes (familial adenomatous polyposis – FAP) and non-polyposis syndromes (familial CRC and Lynch syndrome). Patients with polyposis syndromes can be more easily diagnosed due to their numerous polyps. Patients with Lynch syndrome have sporadic adenomas, making it difficult for recognition.

Various lifestyle and environmental factors correlate with a risk of developing CRC disease, such as increased body weight, smoking, immoderate alcohol consume as well as processed and red meat intake (Botteri *et al.*, 2008; Chan *et al.*, 2011; Cai *et al.*, 2014; Kyrgiou *et al.*, 2017). Despite the fact that patients with type 2 diabetes and patients with CRC show matching risk factors such as increased body weight and reduced physical inactivity, patients with type 2 diabetes continue showing CRC risk even after correcting these factors (Krämer *et al.*, 2012).

Increased risk of CRC is also monitored in persons with pervasive inflammatory bowel disease such as Crohn's disease and ulcerative colitis (Johnson *et al.*, 2013).

1.3 Pathophysiology of CRC and metastatic spread

The process of CRC begins in building an anomalous crypt, which will evolve into a polyp (neoplastic precursor), and eventually in CRC in a process estimated in a 10–15-year period. Currently, it is assumed that the majority of CRCs have cancer stem cells or cancer stell-cell-like cells as cells of origin. The cancer stem cells are found in the base of the colonic crypts and can be initiated by the inactivation of tumour-suppressor genes and by activating oncogenes (Medema, 2013; Nassar and Blanpain, 2016).

Depending on the mutation genesis, CRC can be divided into sporadic, inherited, or familial.

Two major development pathways of the neoplastic precursor lesion are the adenoma-carcinoma pathway, being in charge of 70 – 90 % of CRC, also known as the chromosomal instability (CIN), and the serrated neoplasia pathway, leading to 10 – 20 % of CRC. Another pathway explained is the microsatellite instability (MSI) pathway caused by the loss of DNA repair mechanisms. More than 95% of all CRCs are adenocarcinomas; the rest are mainly neuroendocrine tumours and small cell carcinomas (Akkoca *et al.*, 2014).

Different molecular, anatomical, embryological, histological, and biological characteristics are known when comparing a right-sided (caecum, colon ascendens, and right colon flexure) colon cancer (CC) with a left-sided (left colon flexure, colon descendens, and colon sigmoideum) CC and rectal cancers (RC), which play critical roles in the different metastatic spread.
The blood from the colon and the proximal part of the rectum is drained through the portal vein to the liver. Therefore, CRC from these parts would primarily spread metastatic deposits in the liver. The distal part of the rectum overlaps the portal vein system and is drained in the Vena cava inferior and then to the lungs, spreading metastatic deposits to the lungs (Riihimäki *et al.*, 2016a). Further, tumours originating from the right colon are associated with elevated prevalence of rat sarcoma viral oncogene homolog (RAS), v-raf murine sarcoma viral oncogene homolog B (BRAF) mutation, as well as MSI (Benedix *et al.*, 2012; Kalantzis *et al.*, 2020).
20 to 25% of patients diagnosed with advanced CRC will present colorectal liver metastasis (CRLM) at the time of the diagnosis, a ‘synchronous’ spread. Further, 40 to 50% of CRC patients will usually develop CRLM, a ‘metachronous’ spread, within three years of the initial surgery (Stangl *et al.*, 1994) (Donadon *et al.*, 2007).

When observing organs excluding the liver, additional patterns of metastatic spread are being recognised. CCs (adenocarcinomas, signet ring, and mucinous)

mainly spreads metastasis within the peritoneum, and RCs metastasises to the thorax, bone, and nervous system (Riihimäki *et al.*, 2016a).

1.4 Diagnostic and staging of CRC

Colonoscopy is a method of choice for diagnosing CRC. It can be used simultaneously as an imaging technique and as an interventional method, mainly to remove polyps, perform biopsies, and mark a suspect lesion for surgery. Optimal bowel preparation is essential to ensure high detection of very subtle lesions of the colon mucosa, as such lesions can be early CRC.
In case of an incomplete colonoscopy, a complementary imaging method for detecting CRC or polyps is computed tomography (CT) colonography (Nasseri and Langenfeld, 2017).

A newly diagnosed patient with CRC should undergo an initial staging of CRC in order to determine the cancer's stage and a positive or negative metastatic spread, which has a large impact on the overall prognosis and on the treatment strategy.
Modern imaging of CRC involves several modalities, such as contrast-enhanced CT, magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT.
Using CT as a staging modality is nowadays essential. It provides necessary information, such as the absence or presence of distant metastasis, assessment of the primary tumour and its extension in the adjacent structures, and enlargement of the locoregional or distant lymph nodes.
Although CT is still the most used modality in detecting CRLM (Biasco *et al.*, 2006), the use of modern high-field MRI has dramatically increased in assessing and differencing liver lesions, staging of CRLM, and therapy planning. The use of MRI shows a superior position among the other modalities in the local staging of RC. With the help of MRI, the local extension of RC can be accurately defined, as well as the involvement of the mesorectal fascia and the sphincter complex. Significantly, MRI shows a 94% specificity in the involvement of the circumferential resection margin (Nasseri and Langenfeld, 2017).

If some lesions are still considered suspicious after a CT and MRI scan, using a PET/CT can help in further evaluation, providing information that can change the course and therapy of the disease (Niekel, Bipat and Stoker, 2010).

Nowadays, CRC staging is mainly based on the TNM Staging System, which was adopted by the American Joint Committee on Cancer (AJCC) and Union International Cancer Control (UICC).
The TNM staging system is based on three criteria: T – primary tumour staging, N – nodal status, and M – Metastasis.
Primary tumour staging (T) is furthermore assessed in:
Tx – primary tumour cannot be assessed;
T0 – no evidence of primary tumour,
Tis – carcinoma in situ;
T1 – tumour invading submucosa;
T2 – tumour invading muscularis propria;
T3 – tumour invading the subserosa or into pericolorectal non–peritonealised tissue;
T4a – tumour penetrating into the visceral peritoneal layer;
T4b – tumour invades or is adherent to the adjacent organs.

The nodal status (N) is divided into:
Nx – lymph nodes cannot be assessed;
N0 – there is no evidence of lymph nodal involvement;
N1a – one regional lymph node involved;
N1b – involvement of 2 or 3 regional lymph nodes;
N1c – tumour deposits in the subserosa or involving the non-peritonealised pericolic/perirectal tissue without regional nodal metastasis;
N2a – 4 to 6 lymph nodes involved;
N2b - ≥7 lymph nodes involved.

The presence of metastasis (M) is described with:
Mx – the presence of metastasis cannot be assessed;

M0 – no distant metastasis;
M1a – evidence of distant metastasis to only one organ but without peritoneal metastases;
M1b – evidence of distant metastases involving more than one organ but without peritoneal metastases;
M1c – metastases to the peritoneum, with or without distant metastases in the other organs

1.5 Therapeutic options for CRLM

Three major therapeutic categories in the treatment of CRLM are systemic therapy, surgery, and interventional oncology. According to the stage of the disease, these therapeutic options can be used as a single treatment or in combination. A crucial part of the therapy's planning is deciding whether the treatment will be curative or palliative based on the tumour burden.

1.5.1 Systemic Therapies of CRLM

Chemotherapeutical agents can derange the cell cycle using various mechanisms that produce cell death in fast-dividing cells. Chemotherapy is regularly used as adjuvant therapy in CRLM (Mitchell, Puckett and Nguyen, 2019). Conventional chemotherapeutical agents involve fluorouracil (5-FU), capecitabine, irinotecan, leucovorin, and oxaliplatin (Maher *et al.*, 2017). Usually, these chemotherapeutical agents are administered in combination with fluorouracil, such as FOLFOX (folinic acid, 5-FU, and oxaliplatin) and FOLFIRI (folinic acid, 5-FU, and irinotecan) (Khoo *et al.*, 2016).

According to the European Society For Medical Oncology **(**ESMO) clinical practice guidelines, systemic therapy differs in managing resectable / potentially resectable CRLM and advanced metastatic disease without potential conversion. The ESMO recommendations for potentially resectable CRLM suggest that patients with resectable metastases and favourable criteria may not need

perioperative systemic treatment. For those with uncertain prognosis, oxaliplatin-based chemotherapy is recommended. Further, patients unresponsive to first-line chemotherapy should still be considered for metastasis resection or ablation as well as Transarterial chemoembolisation (TACE) therapy may be an option to achieve hepatic resection. Anti-epidermal growth factor receptor (EGFR) antibodies are suggested for left-sided RAS-wildtype in patients aiming for complete resection. For right-sided and RAS-mutant disease, FOLFOXIRI–bevacizumab is preferred, depending on patient tolerance (Cervantes *et al.*, 2023).

In managing advanced CRLM, assessing the RAS mutational status through biopsy or liquid biopsy is essential for making informed treatment decisions. For most patients, the initial treatment typically includes chemotherapy doublets such as FOLFOX, FOLFIRI, or Capecitabine combined with Oxaliplatin (CAPOX), alongside an anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Anti-EGFR monoclonal antibodies can also be paired with FOLFOX or FOLFIRI doublets. Biological therapy in combination with chemotherapy is advised as the first-line treatment unless there are contraindications. Patients who begin treatment with an oxaliplatin-based regimen are generally recommended to switch to an irinotecan-based therapy or monotherapy as a second-line treatment. Similarly, those initially receiving irinotecan-based therapy may be treated with an oxaliplatin-based regimen (FOLFOX or CAPOX) in the second line, provided there are no contraindications. Patients who have previously undergone irinotecan–fluoropyrimidine-based chemotherapy alone are advised to receive a combination of FOLFOX–bevacizumab. Bevacizumab can be paired with a fluoropyrimidine-doublet that includes either oxaliplatin or irinotecan, based on the initial chemotherapy regimen. For third- and subsequent-line treatments, reintroducing the initial induction therapy may be considered after second-line therapy, assuming there was no disease progression during the first-line chemotherapy's initial induction phase. Regorafenib and Trifluridine-tipacil are recommended for patients who have previously been treated with fluoropyrimidines, oxaliplatin, irinotecan, and biologics, or in earlier therapy lines

following the failure of oxaliplatin and irinotecan regimens. For RAS-wildtype and BRAF-wildtype patients who have not been previously treated with EGFR antibodies, cetuximab and panitumumab are recommended as monotherapies. (Cervantes *et al.*, 2023).

Despite all positive treatment results with chemotherapy, there is an association between chemotherapy and hepatotoxicity. Complications, including steatosis, steatohepatitis, sinusoidal or systemic toxicity, can affect patient outcomes and can enlarge morbidity and mortality after treatment with chemotherapy only and/or surgical resection of CRLM (Zorzi *et al.*, 2007).

1.5.2 Surgery of CRLM

Operative approaches cover open techniques or laparoscopy and anatomic or non-anatomic surgical resection.

Recent advanced surgical procedures, as well as new effective systemic therapies, have expanded the rates of surgical approaches to CRLM in many patients. Hepatectomy, as a gold standard in CRLM, has shown numerous positive clinical outcomes not only in the treatment of solitary lesions but also in the therapy of bilobular nodules and has shown a favourable 30% - 35% at 5-year overall survival in patients with R0 resection (Abdalla *et al.*, 2006; de Haas *et al.*, 2011a).

The goal of hepatectomy is to provide a histologically negative margin or R0-surgical margin. Some studies showed that there is no significant difference in recurrence rate, morbidity, mortality, or survival comparing anatomical to nonanatomical liver resection (Lalmahomed *et al.*, 2011). But, nowadays, the focus has shifted in preserving the liver parenchyma instead of focusing on the tumor volume (Charnsangavej *et al.*, 2006) using parenchymal-sparing methods.

In patients with greater tumour burden, new options can be offered like repeated hepatic resection, portal vein embolisation, and conformity of close resection margins (Zorzi *et al.*, 2006; Lalmahomed *et al.*, 2011).

Further, in the conquest of treating complex patients with bilobular lesions, many other surgical techniques evolved and are used, including two-stage hepatectomy, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), and ultrasound (US) guided enhanced one-stage hepatectomy (e-OSH) (Torzilli *et al.*, 2017) as well as trans-hepatic liver venous deprivation – combined both portal and hepatic vein embolisation (Guiu *et al.*, 2016). Knowing that post-hepatectomy liver failure is the leading cause of mortality after surgical resection and also a notable limitation in executing major liver surgery, portal vein embolisation is also used as the standard of care in inducing liver hypertrophy (Cassese *et al.*, 2022).

1.6 Interventional oncology for treatment of CRLM

Interventional oncological or minimal-invasive image-guided therapies for treating CRLM are divided into two groups: a local percutaneous approach and a vascular catheter-based approach. The group of the local percutaneous approach is then divided into thermal and nonthermal ablative modalities.
The vascular catheter-based approach group includes modalities that use transarterial approaches with the local application of chemotherapies or radioactive microspheres followed by embolisation of the tumour-feeding arteries.

1.6.1 Thermal and nonthermal ablative modalities

Local ablative modalities can achieve tumour destruction using thermal (heat or cold) or nonthermal energy mechanisms. The most commonly used thermal modalities are radiofrequency ablation, microwave ablation, cryoablation, and laser ablation. Irreversible electroporation is a commonly used nonthermal technique.

An emphasis is given to microwave ablation, and it is described separately.

1.6.2 Radiofrequency ablation

Radiofrequency ablation (RF) uses a source of electromagnetic energy within the spectrum of RF (375 – 500 KHz), converting it into heat in the target lesion and achieving tumour destruction (Brace, 2010). An alternating electric field is produced in the tissue around the electrode needle, causing tissue electrons to move in that direction through a closed-loop circuit. As a result of high electrical resistance, frictional heat will be produced. A monopolar or bipolar electrode can be inserted into a tumour using one or more grounding pads (Sommer *et al.*, 2013).

1.6.3 Cryoablation

Cryoablation was one of the first ablation techniques used in treating liver metastasis from colorectal origin. As the name describes, freezing temperatures were used to produce tumour damage. High and rapid freezing temperatures produce cell apoptosis through mechanical damage of the cell and the surrounding blood vessels due to crystallisation and recrystallisation (Rubinsky *et al.*, 1990; Gage and Baust, 1998).
The most used cryoablation systems use special hollow cryoprobes filled with cryogen (cooled gas) that expand at the top of the probe and produce rapid freezing of the treated area.

1.6.4 Laser ablation

Laser ablation uses light energy to achieve hyperthermia through photon absorption of target tissue, causing cell damage and building coagulation necrosis. Multiple laser application technologies are available on the market, which can be divided into superficial or transcutaneous application methods. The term Laser interstitial tumour therapy (LITT) refers to laser energy transmission into target tissue applied through flexible thin fibbers (Ahmed *et al.*, 2014).

1.6.5 Irreversible electroporation

Irreversible electroporation (IRE) is a nonthermal method that uses a pulsed electric field to produce irreversible cell injury. It is based on the phenomenon of 'electroporation', where an externally conducted strong electric field between thin needles promotes cell membrane permeabilisation, causing cell death (Neumann *et al.*, 1982). Although IRE showed mainly minor complications and is unaffected by the 'heat-sink' effect, the method should be done under general anaesthesia with an additionally synchronised electrocardiogram, making it more time-consuming than the other ablative methods.

1.7 Microwave Ablation

Microwave ablation (MWA) is nowadays one of the main techniques used in the local percutaneous approach for the treatment of liver metastases of colorectal origin. The underlying mechanism of MWA is to induce tumour destruction by producing local hyperthermia, achieving an irreversible protein denaturation resulting in coagulative necrosis.

The microwave ablation technique uses electromagnetic waves emitted from a particular antenna to try to develop heat in the target malignant tissue based on the mechanics of dielectric hysteresis. One or, rarely, more coaxial antennas are introduced percutaneously in the target tumour, inducing high-frequency electromagnetic fields (915 MHz or 2,45 Hz) (Vogl *et al.*, 2017).

During microwave ablation, the rapidly alternating electric fields will cause a rotation of water and other polar molecules trying to realign with the induced electric field. This process generates kinetic energy in the target tissue, and as a result, heat well over 100 °C will be produced. Because of the high heat, permanent protein damage and irreversible destruction of mitochondrial and cytosolic cell enzymes will happen. The surrounding tissue near the antenna will desiccate and char, which will lead to forming a coagulative necrosis (Meloni *et al.*, 2017). A complete treatment involves the target lesion and a 5-10 mm margin, parallelly sparing vital or healthy adjacent structures (Ahmed *et al.*, 2014).

1.7.1 Heat sink effect

Blood flow in the surrounding tissue can negatively interact with the heat produced during microwave ablation by cooling the heated tissue. The term heat sink effect alludes to the buffering reaction of a nearby blood vessel (with a diameter > 3mm) adjacent to the ablative area. Consequently, the shape of the ablative area is altered with shrinkage of the overall ablation area size, which can lead to incomplete ablation (Lu *et al.*, 2002).
Some experiments have shown that reducing hepatic perfusion can also reduce the heat sink effect using pharmacological and mechanical strategies (Goldberg *et al.*, 1998; Takamura *et al.*, 2001).
Intermittent clamping of the target vessel also reduces the heat sink effect, but increased vascular and biliary complications have been reported (Van Duijnhoven *et al.*, 2006).

In the course of surgical liver procedures, blood flow is generally controlled by applying the Pringle manoeuvre (Aragon and Solomon, 2012). In interventional radiology procedures, the same manoeuvre can be reproduced by using special balloon occlusion catheters. Such catheters can be percutaneously inserted, producing an occlusion in a segmental portal branch or a hepatic vein (de Baere *et al.*, 2002).

1.7.2 Ablative Margin

The term ‘ablative margin’ or ”safety margin” has been introduced to describe an ideally ablative area surrounding the tumour tissue similar to the surgical ‘resection margin’ to achieve complete tumour ablation and reduce the rate of local tumour progression An ideally ablative margin using microwave ablation of a liver lesion should range between 5 mm and 10 mm in the healthy surrounding tissue.

Many authors are declaring “A0” – Ablation as a complete Ablation of a target lesion with an ablative safety margin from 5 mm to 10 mm, compared to a surgical R0 margin, but currently, data are lacking regarding a definitive recommendation of the ideal ablative margin size (Shady *et al.*, 2018) (Kim *et al.*, 2010; Wang *et al.*, 2013).

In larger tumours (i.e., > 3 cm) where extensive coagulation necrosis and big ablative margins are desired, facing a technical limitation, a multiple needle/antenna approach with 3D planning is sometimes used. This approach is intended to treat large lesions in a single session (Laimer, Schullian and Bale, 2021).

While an extensive ablative margin is advantageous in a curative microwave ablation, a smaller size of the ablative margin is sometimes desired in order to spare a sensitive organ or structure.

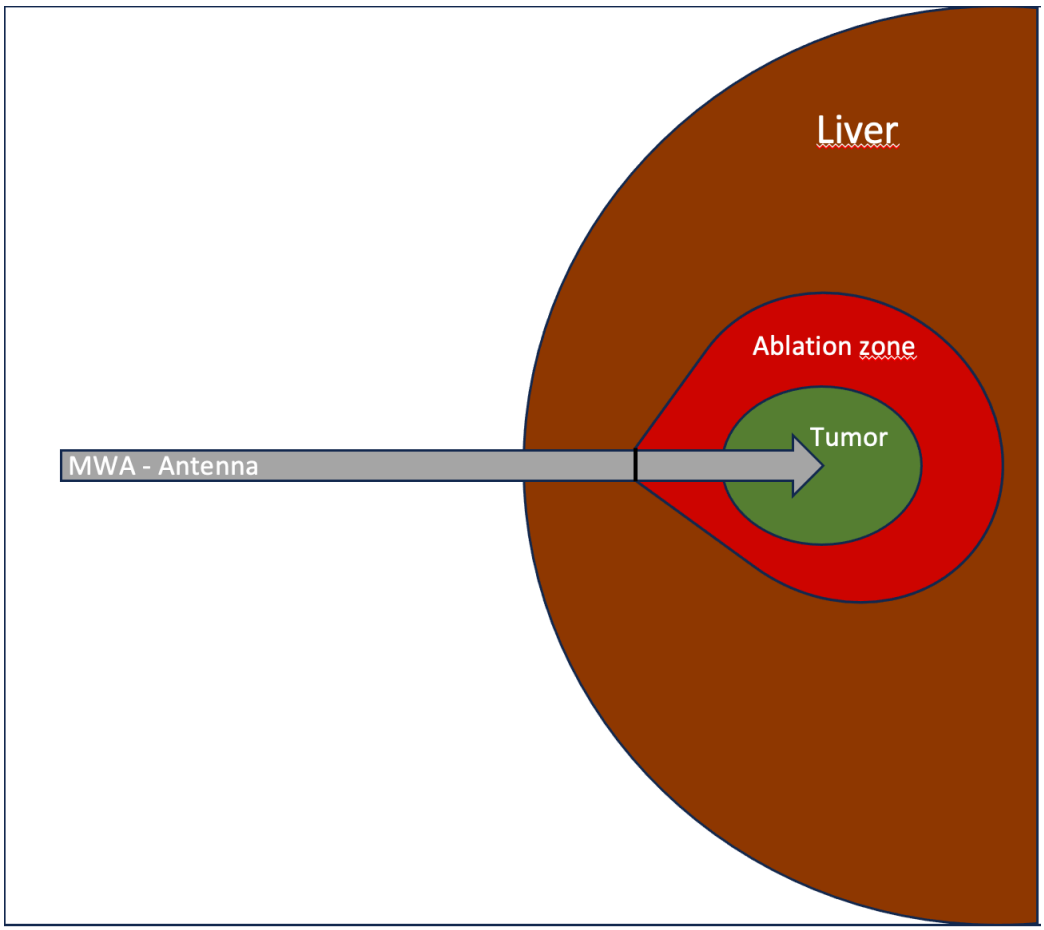


Figure 1: Illustration shows an ideal ablation zone surrounding the whole tumour reaching safety margins.

1.7.3 Microwave ablation system

Microwave ablation systems are made of three main components: the generator, power distribution system/cable, and applicator antenna.

1.7.4 Microwave ablation generators

Microwave ablation generators basically use two power sources to produce energy: magnetron and solid-state amplifiers.
A magnetron-based MWA generator produces electromagnetic energy using a resonant cavity in which electrons are accelerated through a magnetic field. The magnetrons are highly efficient with high output powers, commonly >10 kW, but they demand a high-voltage power supply and, therefore, large and heavy transformers, increasing the overall size of the generator.
Solid-state generators use amplifiers to crate power in stages. They have a lower efficiency but are very stable, producing power output < 150 W, and are smaller in size compared to magnetron-based MWA generators. As a result of a lower efficiency, the solid-state generators are producing large amounts of heat that need to be dispelled.

1.7.5 Power distribution system

The power distribution systems carry the electromagnetic energy from the generator to the applicator antenna in transmission lines. One of the most favoured distribution systems is the coaxial transmission line (coaxial cable) made of a jacket and three inner layers: an outer conductor, dielectric material, and an inner conductor. The coaxial cable has many strengths, such as excellent propagation characteristics, flexibility, and compact size. However, coaxial transmission lines are restricted in their capacity to distribute large amounts of energy.

Amplitude modulators/switches, phase shifters, and power splitters are other components that can be part of the power distribution system.

1.7.6 Microwave antennas

Microwave antennas come in several designs and diverse formats that can transfer energy from the generator to the target tissue. The basic requirements of a microwave antenna should cover minimally invasive features, high efficiency, and creating large zones of heating into the target tissue.

The performance of a microwave antenna can be described using two metrics:

Reflection coefficient - explains the efficiency of power transfer of the antenna, the lower the coefficient, the higher the efficiency of power transfer into the target tissue.

SAR heating pattern: Most microwave antennas produce a teardrop-shaped or ellipsoidal heating pattern, but a perfectly spherical heating pattern is ideal for an interstitial antenna.

As the transfer of energy produces heat that should be dissipated, internal cooling of the antennas has been introduced, and it has been a very important part of MWA systems to reduce shaft heating (Lubner *et al.*, 2010; Yu and Liang, 2017).

1.7.7 Ablative procedure (Image planning, guidance, targeting, technical success, complications and follow-up)

1.7.7.1 Image planning and guidance

Different imaging techniques such as CT, MRI, and US can be used for diagnosis and assessing a target lesion, as well as guidance during a microwave ablation procedure. Particularly important imaging aspects include tumour location, size, shape, and number. As mentioned, location relative to critical adjacent structures or blood vessels that can be at risk for damage is a very important factor in planning an ablative procedure.

1.7.7.2 Targeting

Targeting describes a step-by-step placement of an antenna into the target lesion using intraprocedural image guidance. Nowadays, the microwave ablative procedure is mainly guided by native or contrast-enhanced CT, US, or MRI. Ideal aspects of targeting a specific lesion include the surrounding anatomy and clear lesion presentation combined with multiplanar real-time imaging and interactive options. For this purpose, combining imaging modalities with the fusion of navigation systems has been developed to increase the accuracy of tumour targeting (Abi-Jaoudeh *et al.*, 2012).

Using multiplanar imaging assistance can help the operator with near real-time intraprocedural antenna repositioning.

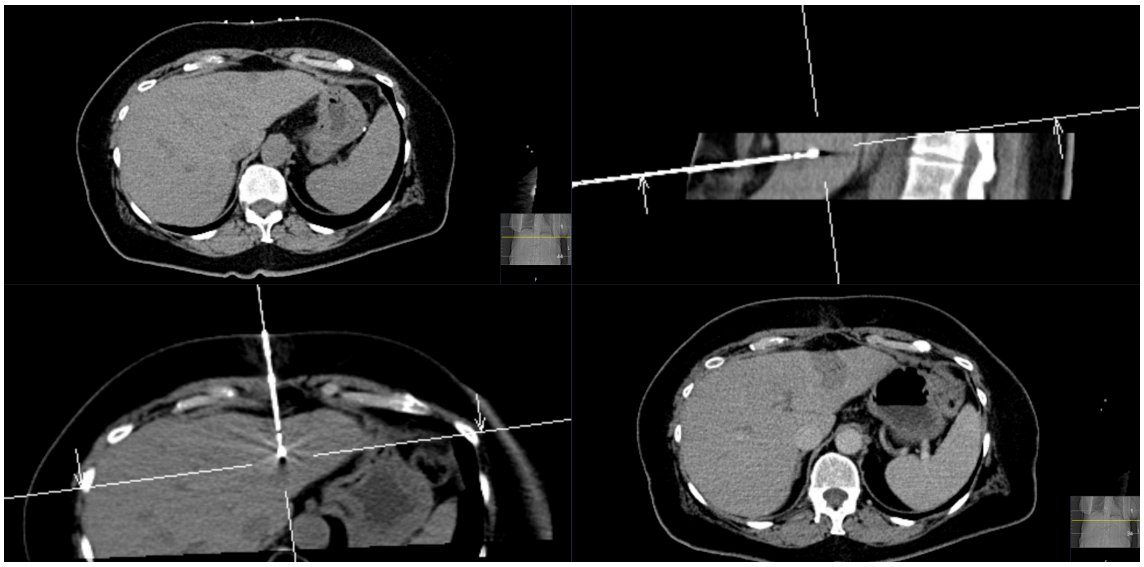


Figure 2: Planning and multiplanar CT-guided step-by-step positioning of a MW antenna in the liver segment III.

1.7.7.3 Technical success

Every given microwave ablation system has its own therapy protocols regarding energy delivery and duration for a target organ or lesion.

The term technical success refers simply to whether the tumour was entirely covered by the ablative area and was treated with the given therapy protocols. Such a procedure will be determined as ‘technically successful’. Using the given

imaging modality, the coverage of the ablation zone can be assessed instantly after the procedure (Ahmed *et al.*, 2011a) (Ahmed *et al.*, 2014).

1.7.7.4 Complications

The most commonly used systems for explaining a complication of the microwave ablation procedure are the Common Terminology Criteria for Adverse Events (CTCAE), the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Classification system, the unified standardised SIR grading system or National Cancer Institute, and the Clavien-Dindo classification system (Sacks *et al.*, 2003) (Clavien *et al.*, 2009; Freites-Martinez *et al.*, 2021).

According to the CTCAE Version 5.0, all Adverse Events (AE) are graded from 1 to 5, and each grade explains the severity of the AE (U.S. Department of Health and Human Services, 2017).
Grade 1 is a mild AE, often asymptomatic or with only mild symptoms. No intervention is indicated. Only clinical or diagnostical observation is recommended.
Grade 2 is defined as a moderate AE with limiting age-appropriate instrumental (ADL), where a local or non-invasive intervention is indicated.
Grade 3 complication is severe and defined as a medically significant AE but not instantly life-threatening. In Grade 3 AE, a hospitalisation or prolongation of hospitalisation is needed. There is also a limiting self-care ADL.
Grade 4 is defined as a life-threatening AE where an urgent intervention is desired.
Grade 5 is defined as death related to AE.

All complications can be divided into immediate complications occurring 6 to 24 hours after the ablation, periprocedural complications lasting up to 30 days, and delayed complications (lasting more than 30 days after the procedure).

According to the CIRSE classification system for complications, an AE or complication is defined as an unintended symptom, sign, or disease temporally related to a medical procedure. It may or may not be caused by the treatment. The timing of an AE or complication is defined as intraoperative, perioperative, or delayed (Filippiadis *et al.*, 2017).

Grade 1 is an AE or a complication during the procedure that can be resolved during the same session requires no extra treatment and does not cause a deviation from the normal post-therapeutic process.

Grade 2 is a prolonged observation, including an overnight stay, but no additional post-procedure therapy.

Grade 3 requires prolonged hospital stay or additional post-procedure therapy.

Grade 4 is defined as a complication that causes permanent mild sequelae, and Grade 5 causes permanent severe sequelae.

Grade 6 is defined as death.

1.7.7.4.1 Post-ablation syndrome (PAS)

Following ablation, PAS is a rare, self-limited, and common complex of flu-like illness with low-grade fever, general malaise, and vomiting. The aetiology of PAS is still not strictly defined, but the presumably explanation involves setting free the intracellular material into the bloodstream, creating an immune reaction in the system. The duration of PAS is associated with the volume of the coagulation necrosis as well as the condition of the patient (Dodd *et al.*, 2005).

1.7.7.5 Follow-Up

Primary follow-up should ideally be done within 4 to 6 weeks following the ablation procedure to prove whether a supplementary ablation procedure is required. The most common imaging modalities used for follow-up are contrast-enhanced MRI or CT.

The initial follow-up compares the coagulation necrosis and the ablative margin for further follow-ups and assesses technique efficacy

1.8 Transarterial Treatments

1.8.1 TransArterial ChemoEmbolisation (TACE)

The fundamental principle of TACE is to combine high doses of chemotherapy agents and embolisation of the tumour-feeding arteries, eventually producing tumour necrosis and tumour ischemia (Mahnken *et al.*, 2009). With applying chemotherapy and obstructing the blood flow due to embolisation, a prolonged contact period between the tumour cells and the chemotherapeutical drug is achieved, which is the main aim of TACE. The embolics used in TACE can be divided into three separate groups: conventional TACE (cTACE) using Lipiodol, a product of poopy seed oil as embolic, degradable starch microspheres (DSM), and drug-eluting beads (DEB) (Massmann *et al.*, 2015).

Nowadays, the most used chemotherapy drugs in TACE are Irinotecan, Doxorubicin, Epirubicin, Cisplatin, and Mitomycin (Massmann *et al.*, 2015) (Pereira and Sommer, 2015).

TACE with irinotecan-eluting beads is another choice for treating CRLM, especially when curative treatments aren't an option. An interim Analysis from the CIREL (CIrse Registry for LifePearl™ microspheres) showed that LifePearl-irinotecan (LP-IRI) TACE had a tolerable toxicity profile mainly used as intensification or salvage therapy. The overall health-related quality of life score (HRQOL) worsened for more patients compared to their function and symptom scores. However, for both physical function and symptoms, over 70% of patients reported either stable or improved scores at the first follow-up compared to baseline (Pereira *et al.*, 2021). In the same study, Helmberger et al. reported 99% technical success in all LP-IRI sessions with high tolerability, suggesting that LP-IRI TACE can be used together with concomitant systemic therapy or ablation (Helmberger *et al.*, 2022).

TACE can be combined with other modalities, such as percutaneous ablation or surgery, as well as systemic chemotherapy. TACE is mainly indicated in a

palliative situation but should be generally discussed in patients with a life expectancy > 3 months and with maintained physical capacity (ideally ECOG 0–1) (Geschwind *et al.*, 2002; Lewandowski *et al.*, 2011).

1.8.2 TransArterial RadioEmbolisation (TARE)

The fundamental principle of TARE is the combination of two separate therapeutic functions, namely interstitial radiation therapy and embolisation, using microspheres that are also carriers of the radiation agent. These radioactive microspheres are injected into the liver arteries after transarterial catheterisation and will end in the tumour microvasculature or arterioles and the liver parenchyma. Physiologically, the liver's blood supply is primarily obtained by the V. portae, contrary to liver tumours or metastases, which are mainly vascularised through the liver arteries. This allows superior targeting of hypervascularised liver tumours and restricts radiation of normal liver parenchyma (Lewandowski and Salem, 2006).

Currently, three types of radioactive microspheres are available on the market: 90Y-resin microspheres, 90Y-glass microspheres, and 166 Ho-poly-L-lactic acid (PLLA) microspheres (d'Abadie *et al.*, 2021). These three distinct microspheres have different physicochemical characteristics and produce different biological effects.

Possible contraindications for TARE are impaired liver function or tumour burden of > 50% of the liver parenchyma, complete occlusion der V. portae, or extrahepatic tumour spread (Hoffmann *et al.*, 2011). The main complications of TARE are radiation-induced liver disease and postembolisation syndrome.

1.9 Hypothesis

While randomised clinical trials (RCTs) provide valuable evidence for establishing causal relationships between medical interventions and outcomes, they may not always address the complexities of real-world clinical practice or provide sufficient evidence for guiding healthcare decision-making in interventional radiology (IR). Hence, complementary approaches, such as pragmatic trials, real-world data (RWD) analyses and registry studies, are often used to supplement RCT findings and provide a more comprehensive understanding of treatment effectiveness, safety, and implementation in real-world settings (Wang and Kohi, 2018).

Offering insights beyond controlled clinical trials, RWD and prospective registry studies are crucial in advancing minimally invasive therapies in IR. One of the key advantages of RWD is its ability to capture outcomes in patients who may not have met the strict inclusion criteria of clinical trials. They can also help us to tailor interventions to individual patient needs and anticipate potential challenges that may not have been apparent in controlled trial settings (Kokkotou *et al.*, 2024).
Further, prospective registry studies, in particular, offer a structured framework for collecting standardized data on IR procedures over time. By enrolling patients before undergoing treatment, the registries enable researchers to track long-term outcomes, complications, and trends in procedural techniques. This longitudinal approach allows evaluation of real-world effectiveness and safety profiles, giving continuous quality improvement and development of best practices in IR.
Additional, in situations where a randomized design is unattainable, integrating external control data into the registry study design as an experimental control arm can offer a valuable approach to enhance result interpretation. This allows for both formal and informal comparative analyses (Mishra-Kalyani *et al.*, 2022).

In this study, the RWD concerning MWA in CRLM from the prospective Registry will try to give us more crucial information about the patient's and tumour characteristics and safety. This RWD will attempt to help us understand the patient collective and the tumour features, upgrading our knowledge concerning MWA therapy and the management of patients with CRLM.

2. Methods

2.1 Study protocol

All procedures involving human participants in this prospective multi-centre, observational, single-arm study were accomplished in compliance with the ethical standards of the national and/or institutional research committee and were in accordance with the 1964 Helsinki Declaration.

In Germany, this study was approved by the ethics committee of the University of Tuebingen (Project Number: 871/2019BO2) and the State Medical Chamber of Baden-Wuerttemberg (Project Number: F-2019-081#A2). The first approval was granted on 14.01.2020 and renewed on 09.12.2022.

All patients were informed and gave their written consent before enrolment in the study.

2.2 Study collective

2.2.1 Patients characteristic

CIEMAR is a prospective European-wide observational study analysing inclusion criteria and treatment outcomes of patients with CRLM treated with MWA using the Emprint or Emprint HP device (Medtronic plc Minneapolis, Minnesota). Our study is an interim analysis of the CIEMAR study focusing on the patients' and tumours' characteristics, technical aspects, and safety matters. Patients were recruited in 36 hospitals from 11 different European countries. In total, 500 patients were included. All patients had been diagnosed with colorectal adenocarcinoma with a liver-only or liver-dominant metastatic disease that required MWA of CRLM between 2019 and 2023.

2.2.2 Patient enrolment

Screening for this study required previous recommendations by a multidisciplinary tumour board.

In- and exclusion criteria defined by study protocol NCT03775980
as followed:

‘‘Inclusion criteria:

- ≥ 18 years

- histologically proven colorectal liver metastases or diagnosed by imaging
- treated with Emprint of Emprint HP Microwave ablation system
- patient introduced to MWA by a multidisciplinary tumour board
- signed Informed consent form
- intention to completely treat all detectable diseases within eight weeks using ablation, resection, stereotactic ablative radiotherapy
- maximum number of 9 total liver lesions
- all liver lesions must be locally treatment-naive
- maximum diameter of the largest liver lesion treated with MWA must not exceed 3 cm
- maximum diameter of lesions treated surgically may exceed this limitation
- maximum number of 5 lung nodules eligible to be treated
- patients may receive simultaneous liver resection and microwave ablation
- patients may have received previous systemic therapy
- patients must not have received surgical or thermal ablation for other liver lesions in the last three months before inclusion
- patients treated with a liver-first approach may be included if treatment of the primary tumour is planned
- if applicable: complete response of treated rectal tumour proven by imaging

Exclusion criteria:

- life expectancy less than six months (palliative treatment)
- extrahepatic metastases, with the exception of a maximum of 5 lung nodules
- ongoing infection (viral/bacterial)
- patients receiving simultaneous bowel surgery and microwave ablation
- patients receiving simultaneous IRE, RFA, Stereotactic body radiotherapy (SBRT), cryoablation, High-Intensity Focused Ultrasound (HIFU), or other local treatment than resection
- pregnant women
- patients with liver metastases that cannot be completely and safely treated
- active cancers other than CRC
- non-resected primary CC
- advanced liver disease or evidence of liver insufficiency'' (NCT03775980).

2.3 Informed consent form

All patients were informed at the consultation visit about the possibility of being enrolled in the CIEMAR study, following the recommendation to treat the liver metastases with ablation and other alternative treatments. First, the patients were adequately informed about the registry and the expected clinical outcomes. Second, signing and dating the informed consent form defines enrollment. Every patient received the original informed consent form or a copy of the signed form, depending on the country of enrollment.

All patients received sufficient time to read the informed data/consent release form and to eliminate ambiguities. All forms were given in the patient's native language, containing the following elements:

- purpose of the registry

- general information about the registry and the sponsor
- statement that CIEMAR is an absolutely observational study
- a statement that the patient will be provided with the possibility to voluntarily fill out the quality-of-life questionnaire
- statement that the involvement in the study will not somehow influence the patient's treatment and that it is entirely voluntary
- statement that images will be submitted to the central review
- information on data usage, data preservation, data protection, and pseudonymisation of the data
- information on the patient's rights to leave the study at any time without any consequence of the patient's treatment
- information about the benefits and risks
- information on the patient's rights conferring with EU Regulation 2016/679 (access to and, if necessary, rectification of deletion of personal data, objection or restriction to processing personal data, right to place a complaint with a supervisory authority, right to data movability)
- financial statement
- statement of privacy, including that data may be presented without revealing the patient's identity
- contact information of the Principal Investigator
- A statement of informed agreement/consent to data release was also included.

2.4 Study design - CIEMAR

CIEMAR is a multi-centre, single-arm, prospective, observational (non-interventional) cohort study aiming to gather 'real world' data on MWA of CRLM using the Emprint or Emprint HP microwave ablation device as performed in routine clinical daily practice.

The primary objective is to evaluate the effectiveness of MWA performed with the Emprint or Emprint HP device. The primary efficacy endpoint is to evaluate local tumour control in the liver on a per-lesion basis.
The secondary endpoints include safety, adverse events, overall survival, overall disease-free survival, hepatic disease-free survival, time to untreatable progression by thermal ablation and systemic cancer therapy vacation, quality of life, and economic aspects (Study protocol: NCT03775980).

This large multi-centre study aims to improve the understanding of MWA for patients with CRLM by prospectively exploring the evidence base for the effectiveness and safety of MWA in a large-scale and cross-border cohort. Furthermore, the current evidence base concerning MWA should be extended with suitably defined clinical follow-up data, as well as gathering data concerning quality of life and cost-effectiveness. Moreover, providing a large-scale, multi-centric, international representative cohort that can advise cancer treatment guidelines and help with treatment access by healthcare authorities and insurance companies.

CIRSE is the scientific sponsor of CIEMAR, represented by the CIRSE Executive Board, which has final responsibility for the scientific and ethical aspects of the study.
Medtronic (Medtronic plc, Minneapolis, Minnesota) supported this research financially through a contractually agreed-upon research grant.

Patient enrollment started in September 2019 and was completed in January 2023, with CIEMAR reaching its target of 500 patients.
Centres involved in CIEMAR are requested to follow up patients' end-of-data collection, study exit, or death. To measure the primary endpoint of local tumour control, a follow up time of 12 months is required. For the secondary endpoint, progression-free survival, a minimum follow-up time of 18 months is recommended, hence the minimum meaningful follow-up time per patient is defined as 18 months.

2.4.1 Center selection criteria and enrolment

All participating centres confirmed that they had performed at least 20 MWA of liver metastases per year, using any thermal ablation technique, thus during the last four years, i.e. a minimum of 80 treatment of liver metastases using any thermal ablation modality. Further, they agreed to comply with the registry demands specified in the investigation plan and to participate in all entitled subjects of the registry.

Centres were identified by expert opinion as likely users of Emprint as a standard of care for CRLM. Furthermore, they positively responded to the CIRSE Letter of Intent sent out on the 24th October 2018. All centres received a Centre Qualification Questionnaire to confirm compliance with the above-mentioned selection criteria. To help optimise data collection, the centres provided information about the accessible infrastructures. Every medical centre assigned one accordingly trained medical professional, who had the role of a local Principal Investigator (PI).

After signing the hospital participation agreement by both parties, training, including all aspects of the study, occurred at the centres. Particular training was obligatory for the PI and the staff, using the registry electronic data capture (EDC) platform as well as the registry operating procedures. After completing the necessary training successfully, all PIs received the required CIEMAR study documents and log-in details for the registry platform to enrol patients and enter data.

2.4.2 Data Collection and Monitoring

All PI's and staff members approved by the PI were recognised in the CIEMAR Delegation Form. They received an individual account and log-in information to enter the electronic case report form (eCRF). Each eCRF consisted of various forms categorised and divided by the study events, which consisted of baseline,

treatment, and follow-up 1 to 13, which are mandatory for every patient enrolled in the study. The occurrence of any additional clinical adverse events had to be reported in special forms.

Collecting and submitting clinical and patient-reported quality of life (QoL) data were collected at key treatment time points such as:

- Baseline <- 1 month before treatment
- Treatment – after each treatment
- Concomitant therapies – between pre-MWA and post MWA CT/MRI scan
- Follow-up 1 – within one month after treatment
- Follow-up 2 – 3 months after treatment
- Follow-up 3 – 6 months after treatment
- Follow-up 4 – 9 months after treatment
- Follow-up 5 – 12 months after treatment
- Follow-up 6-13 – every six months thereafter

Timepoints and study events were created to provide adequate data to address all study endpoints.

The Baseline form was evaluated ≤ 4 weeks before the first treatment and included the following parameters: Evaluation date, imaging modality, age, sex, primary tumour diagnosis date, location of the primary tumour, pTNM stadium, previous primary tumour treatments, completeness of previous surgical resection (R-classification), adjuvant systemic therapy, liver metastases diagnosis date, previous metastases treatments, metastases treatment type, primary tumour status (Response Evaluation Criteria In Solid Tumors - RECIST), lung metastases and their number, treatment for lung metastases, performance status – (Eastern Cooperative Oncology Group - ECOG), RAS and BRAF (V600E) mutation, Mismatch repair (MMR) status, Clinical risk – Fong Clinical Risk Score, Carcinoembryonales Antigen (CEA), comorbidity status – Charlson Comorbidity Index (CCI) and QoL.

The treatment form was evaluated on treatment day and included the following parameters:
Lesion ID, the current size of the lesion, location, proximity to a critical structure, status of treated lesion, imaging modality, number of follow-ups, most recent follow-up, number of treatments, most recent treatment, date of the treatment session, treated tumours, type of Emprint generator used, ablation method, number of treated liver metastases, size of largest liver lesion at treatment, procedural medication, anaesthesia type, prophylactic antibiotics, technical success, the reason for not achieving complete ablation, nights in hospital after ablation, the reason for extended hospitalisation, number of probes used during treatment, guidance method used during treatment, ablation time, ablation power and adverse events (upon occurrence).

The follow-up forms (1 to 13) were evaluated as mentioned above. They consisted of the following parameters: Lesion ID, the current size of the lesion, location, proximity to a critical structure, status of treated lesion, imaging modality, number of follow-ups, most recent follow-up, number of treatments, most recent treatment, nights spent in the hospital after ablation, the reason for extended hospitalisation, date of follow-up, date of follow-up imaging, date of assessment of the margin by cross-sectional imaging, imaging method, liver progression, number of new lesions, extra-hepatic progression, location of new lesions, treatment following progression, recurrence in an ablated lesion, residual tumour, ablation margin, ablation margin confirmed, method of ablation margin confirmation, quality of life and adverse events (upon occurrence).

Adverse events were noted upon occurrence and graded using the CTCAE Version 5.0, which is maximally 30 days after treatment.

To estimate the health-related quality of life (QoL) and possible changes after therapy with MWA, standardised cancer-related questionnaires (Version 3) from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 Manual (2001) were used. The QLQ-C30 includes a global health

status / QoL scale, five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom scales (Fatigue, pain, shortness of breath), and six single items (appetite loss, constipation, diarrhoea, insomnia, nausea, vomiting), all measured in a range from 0 to 100.

The patients were asked to complete them at the Baseline visit and Follow-up 1. They were also offered the option of getting the questionnaire in their native language.

Any other clinical event observed was reported in special forms such as:

- Concomitant therapies – upon occurrence
- Date and reason of study exit – upon occurrence
- Loss to follow-up (verification of status alive/dead) – end of study
- Date of last contact – End of study
- Cause and date of death – end of study
- Reason for withdrawal of consent – end of study
- Reason for investigator decision – end of study

The assessment of the primary efficacy endpoint of tumour status at 12 months was executed by each local medical investigator according to the house standard of practice for following up CRLM patients, including CT, MRI, PET CT, PET-MRI or contrast-enhanced US as radiological imaging.

The assessment and report of the secondary endpoints were performed by individual investigators in every centre as maintained by the routine clinical practice.

All clinical data of CIEMAR were pseudonymised and collected by means of an EDC system primarily via an EDC hosted by OpenClinica (OpenClinica, LCC, Waltham, MA, USA). Collected data were kept and encrypted on servers at the AWS-EU Datacentre in Frankfurt, Germany, at a high level of security and Google

Cloud Platform (GCP) compliance (21CFR Part 11 compliant, certified by SSAE-16 Type II SOC II, ISO 90001, ISO 27001 a European General Data Protection Regulation).

The CIRSE Clinical Research Department remotely monitored all data submitted in CIEMAR and managed the data weekly, ensuring high data quality.

2.4.3 Study and Patient Timeline

Patient enrolment started in September 2019 and was completed in January 2023, with CIEMAR reaching its target of 500 patients. To reach the intended long-term follow-up periods, follow-up data collection of enrolled patients will continue for three more years until January 2026.

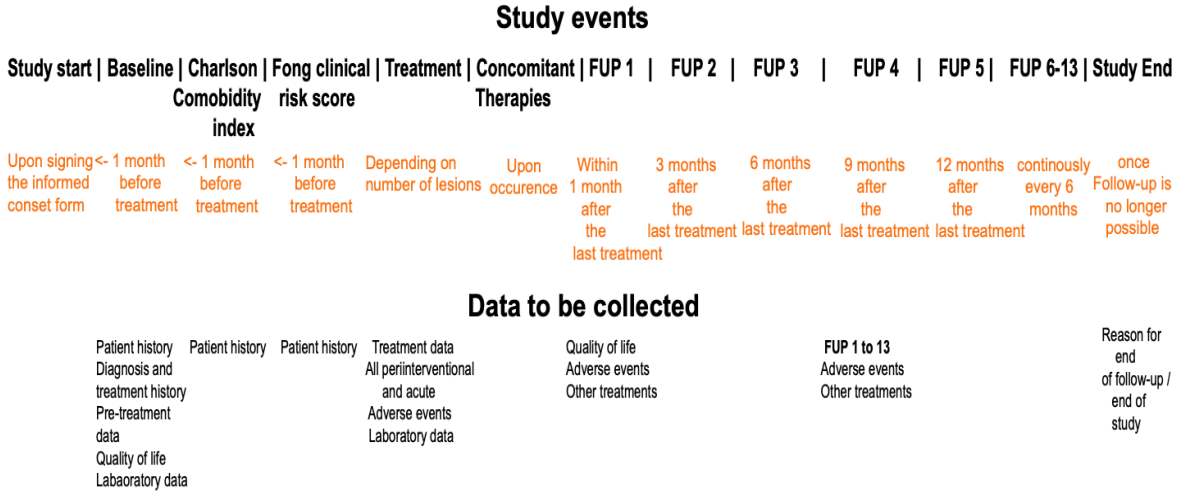


Figure 3: Study and patient timeline.

2.5 Data examination

This dissertation focuses on patients, tumour characteristics, and safety. The data were taken from the Baseline-, Treatment-, Follow-up-1 and the Adverse Events form, and the quality-of-life questionnaires were analysed.

Data examined from the Baseline form included:

- demographics (age, gender)
- primary tumour localisation
- primary tumour stadium
- primary tumour treatments
- systemic therapy
- ECOG - Performance score (PS)
- FONG - score
- CCI
- liver lesions local treatment
- mutation RAS, BRAF, MMR
- lung metastases and their number

Data examined from the Treatment form included:

- the size of the liver lesions
- proximity to critical structure
- liver lesions localisation
- treatment characteristics
- imaging modality
- hospitalisation, number of nights

Data examined from the Follow-ups forms included:

- size of the liver lesions
- proximity to critical structure
- hospitalisation, number of nights

According to CTCAE Version 5.0, the adverse events data were extracted from the Adverse Events form upon occurrence, a maximum of 30 days after every treatment.

Data concerning quality of life were extracted from the QLQ-C30 distributed at the time of Baseline and Follow-up 1.

2.6 Statistical analyses

All categorical data for patients, tumour characteristics, and adverse events are presented as simple counts and/or percentages, along with the number and percentage of missing observations. Further, means and median values are analysed for some of the data.

ECOG-, FONG- and CCI- Scores are presented as a percentage of the sum.

Quality-of-life data results are presented with global health status / QoL score, function score, and symptom score at Baseline and Follow-Up 1. Absolute values and changes are presented using summary statistics and the EORTC QLQ-C30 Scoring manual.

The RawScore (RS) was calculated according to the RS formula where *I* are items included in the scales:

RawScore = RS = $(I_1+I_2+\ldots+I_n)$ / n

To obtain the score S for functional scales, global health status / QoL and symptom scales, linear transformation to 0 - 100 was used:

Functional scales: $S = \{ 1- \frac{(RS-1)}{range} \} \times 100$

Symptom scales/items: $S = \{(RS-1) /range\} \times 100$

Global health status /QoL: $S = \{(RS-1) /range\} \times 100$

The Paired Wilcoxon Rank test was used to show the differences in the scores from Baseline to Follow-up 1.
The summaries were further divided into subgroups, and covariate analyses were performed applying analysis of covariance (ANCOVA).

The number of missing data is included in the total.

The statistical data analyses were performed with RStudio (Version 4.2.2).

3. Results

This interim cohort study analysed data of 500 patients with liver metastasis from rectal or colon cancer origin who underwent a MWA of the liver metastases. The study emphasises patient and tumour characteristics and the safety of MWA as a therapy method.

3.1 Patient characteristics

Out of all 500 patients, 175, or 35%, are female, and 322, or 65%, are male. The youngest patient is 29 years old, and the oldest patient is 92 years old. The mean age of the patients is 66. Data is missing for 3 patients.

3.1.1 ECOG - Performance status

Most of the patients were fully active and could carry on all pre-disease performances without restriction, whereas 69% of the patients presented an ECOG score of 0. ECOG score of 1 had 20% of the patients, and only 3% showed an impaired ECOG score of 2 to 4.

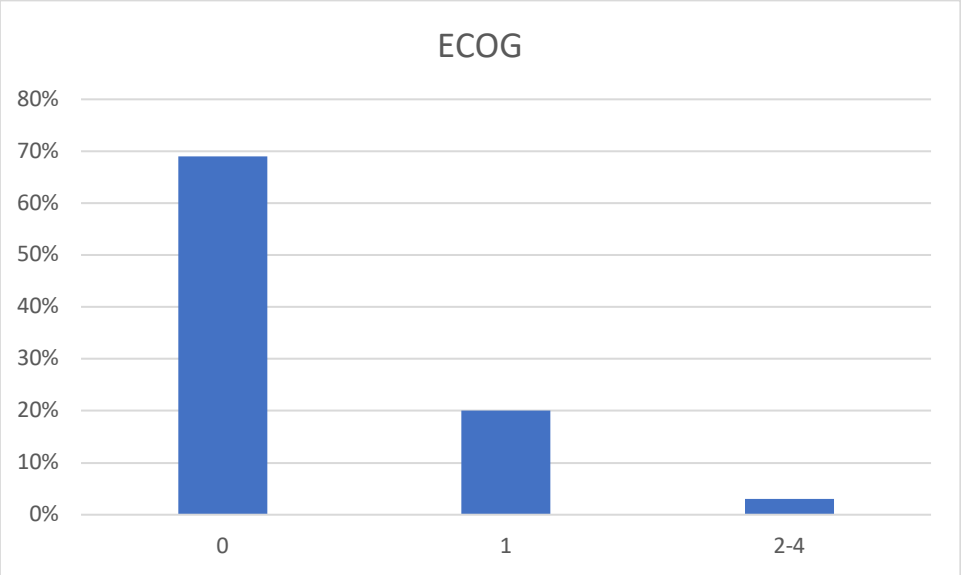


Figure 4: ECOG – Performance status.

3.1.2 Fong – Score

Considering ablation for patients unsuitable for surgery according to the Fong score, 72 % of the patients showed a Fong score of 2 and 3; of them, 40% had a score of 2 and 32% score of 3, meaning a medium preoperative risk. 5% of the patients had a Fong score of 0, and 21% had a Fong score of 1, sensing low preoperative risk. 2% of the patients had a high risk for surgery with a Fong score 4.

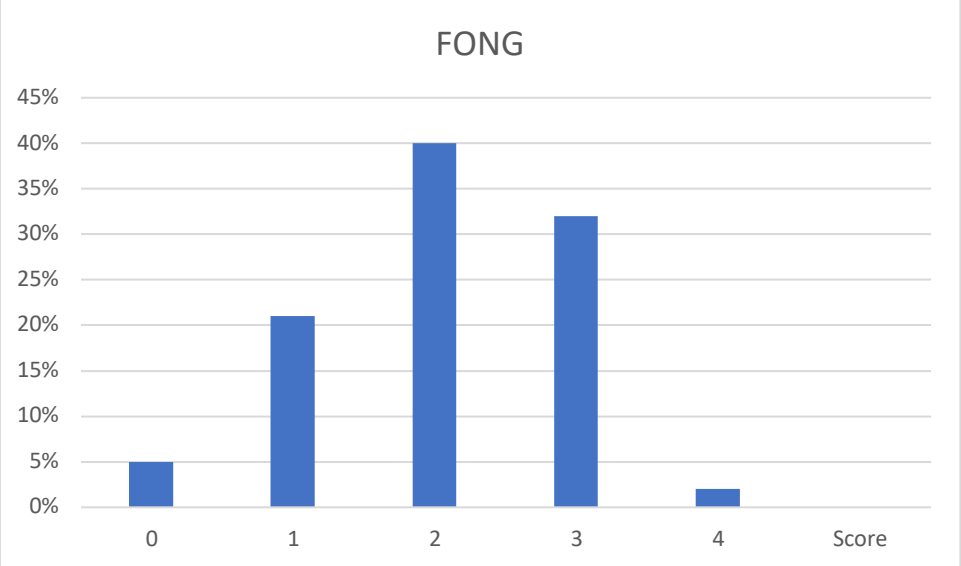


Figure 5: FONG - Score

3.1.3 Charlson comorbidity index (CCI)

In our study, only 19% of the patients had a severe CCI Score of 5 to 17. 37 % of the patients showed a moderate CCI score of 3 to 4. Mild CCI Score had 44% of the patients, where 9% had a 0 CCI score, 16% had a CCI Score of 1, and 19% had a CCI Score of 2.

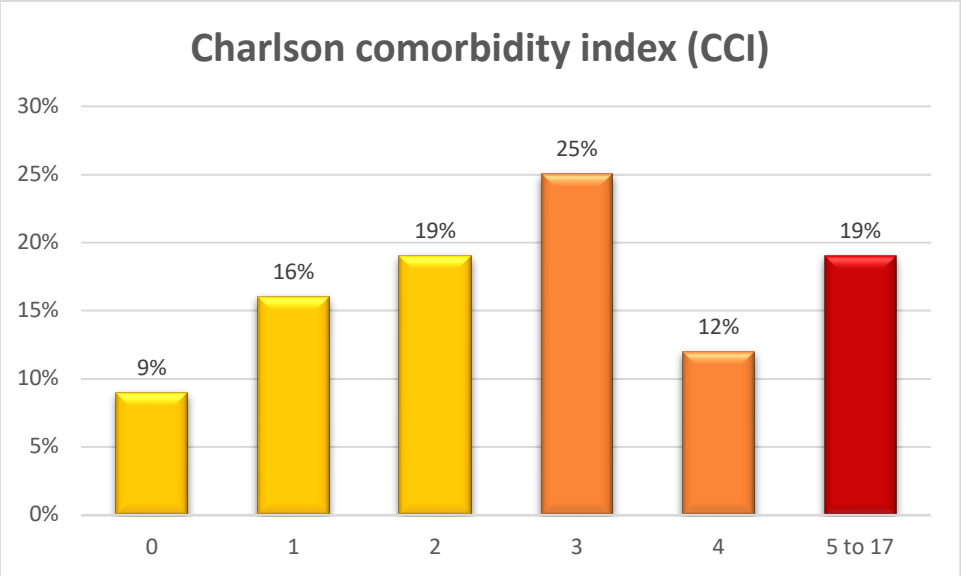


Figure 6: Charlson comorbidity index (CCI)

3.2 Tumour characteristics

3.2.1 Primary tumour characteristics

3.2.1.1 Localisation

Most of the patients – 194 had a tumour in the left colon after the splenic flexure. Tumours of the right colon or before the splenic flexure had 131 patients. 173 of the patients had a rectum tumour from the anal verge to 15 cm above.

Data is missing for 2 patients.

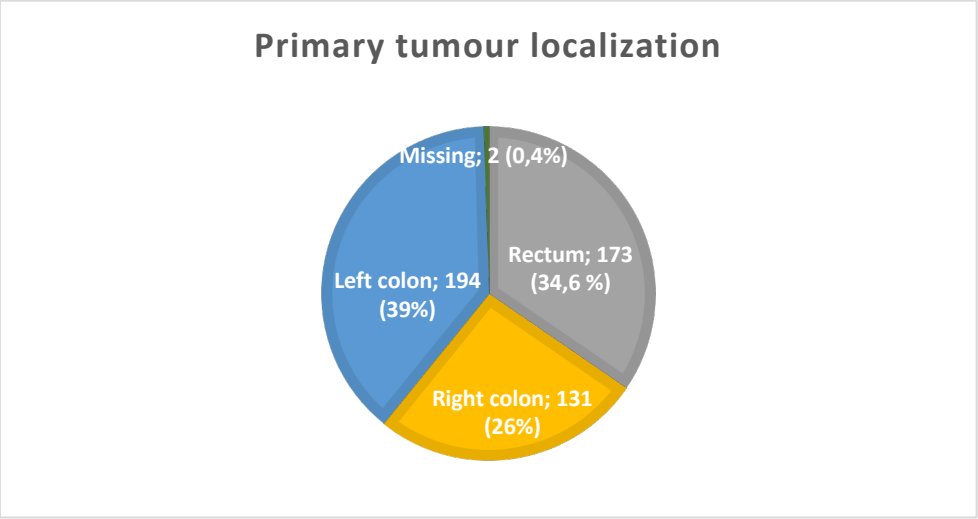


Figure 7: Localisation of the primary tumour (CRC)

3.2.1.2 TMN – Staging system

All patients were staged according to the TMN Staging system.

T – Stadium

Tis had 5 or 1% of the patients.

T1-Stadium 14 patients or 3%.

T2-Stadium 45 patients, 9%.

Most of the patients had a T3 tumour stadium, making 60% of all patients.

T4-Stadium showed 100 patients or 20%.

Data is missing for 7% of the patients.

N – Stadium

25 % of the patients, or 125 of them, had N0-stadium.

N1a – stadium had 91 patients, or 18%.

N1b – stadium 84 patients, 17%.

31 patients, or 6%, had N1c – Stadium.

N1x – stadium had 23 patients or 5%.

N2a – stadium 92 patients, 18%.

Nx 13 patients, 3%.

Data is missing for 8% of the patients.

M – Stadium

M0 had 145 patients, 29%.

Most patients showed M1 – Stadium, 277 patients, 56%.

Mx had 46 patients, 9%.

Data is missing for 6% of the patients.

3.2.1.3 Primary tumour treatment

The majority of the patients, 387 patients, or 78%, underwent surgical treatment for the primary tumour. 99 patients underwent radical

radiotherapy/radiochemotherapy, making up 20 % of the patients. Data is missing for 14 patients, or 2%. After surgical removal of the primary tumour, a greater number of the patients—341—showed R0 or no residual tumour. 235 patients had undergone adjuvant chemotherapy after successful resection of the primary tumour.

3.2.2 Liver Lesion Characteristics

3.2.2.1 Number of liver lesions and size

A total of 1174 liver lesions were reported.
The smallest lesion measured 0,1 cm, and the biggest liver lesion measured 7,3 cm. The median size of the lesions is 1,5 cm.

3.2.2.2 Localization of the liver lesions

In liver segment I, there were 15 lesions, or 1% of all lesions. 108 lesions were reported in liver segment II, or 9%. In liver segment III, there were 73 lesions, or 6%. In the liver segment IVa, 135 lesions were described, making up 12% of all lesions. In liver segment IVb, 41 lesions or 4% of all lesions were reported. Liver segment V has 119 lesions, 10%. In liver segment VI, there were 179 lesions, or 16%. Most of the lesions were in liver segment VII and VIII, in liver segment VII – 218 lesions making 19 % and liver segment VIII – 253 lesions making 22% of all lesions.
Data is missing for 32 lesions.

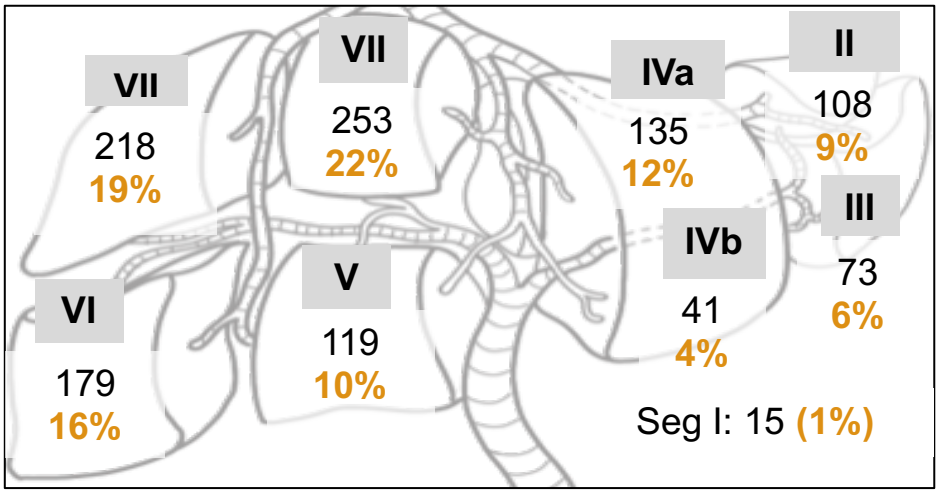


Figure 8: Localisation of CRLM in the liver segments

3.2.2.3 Proximity to critical structure

Location adjacent to a critical structure for MWA showed 215 lesions.
113 lesions were adjacent to large vessels. 10 lesions showed proximity to the bile duct. 9 lesions were close to a near bowel. 13 lesions showed proximity to the stomach. 2 lesions were near the right adrenal gland. 57 lesions showed closeness to the diaphragm. Nine lesions showed proximity to the heart, and 2 lesions were close to the gall bladder.

3.2.2.4 Liver lesions mutation and metastatic spread

RAS MUT showed 136 lesions, RAS WT showed 160, BRAF MUT showed 25 lesions, and BRAS WT showed 231 lesions. MMR MSS showed 197 lesions, and MMR MSI showed 17 lesions.
A synchronous metastatic spread showed 127 lesions. 358 lesions showed a metachronous metastatic spread.

3.2.2.5 Previous Liver Treatments

222 of the patients underwent a systemic chemotherapy treatment concerning the liver metastatic disease before MWA. Another 150 patients faced surgical

resection of the liver metastasis. Only 66 patients had a previous Ablation of the liver lesions, of which 54 patients had a microwave ablation and 12 patients underwent a radiofrequency ablation. 12 patients underwent a transarterial treatment before ablation.

3.3 Lung metastasis

Lung metastases had 59 patients. 34 patients, or 58% of them, had only 1 or 2 lung metastases. Three to 5 lung metastases showed 22 patients or 37%.
Approximately half of the patients, 29 patients, had no treatment for lung metastasis. 26 metastases underwent treatment. 10 metastases were removed with surgery. 8 metastases underwent a lung ablation, of which 6 had an MWA, 1 RFA, and data is missing for 1 metastasis. One metastasis SBRT.

3.4 Safety

3.4.1 Guidance method

The majority of the lesions—86%—treated with MWA were done with a CT or US as a navigation method; from them, 50% underwent CT-guided and 36% US-guided MWA. MRI as a guiding method was used only in 1% of the lesions. Surgically guided MWA had 2% of the lesions. Only 61 lesions were treated simultaneously with MWA ablation and surgical resection.
Real time fusion imaging guidance was used in 8% of the lesions. Robotic guidance became 2% of the lesions.

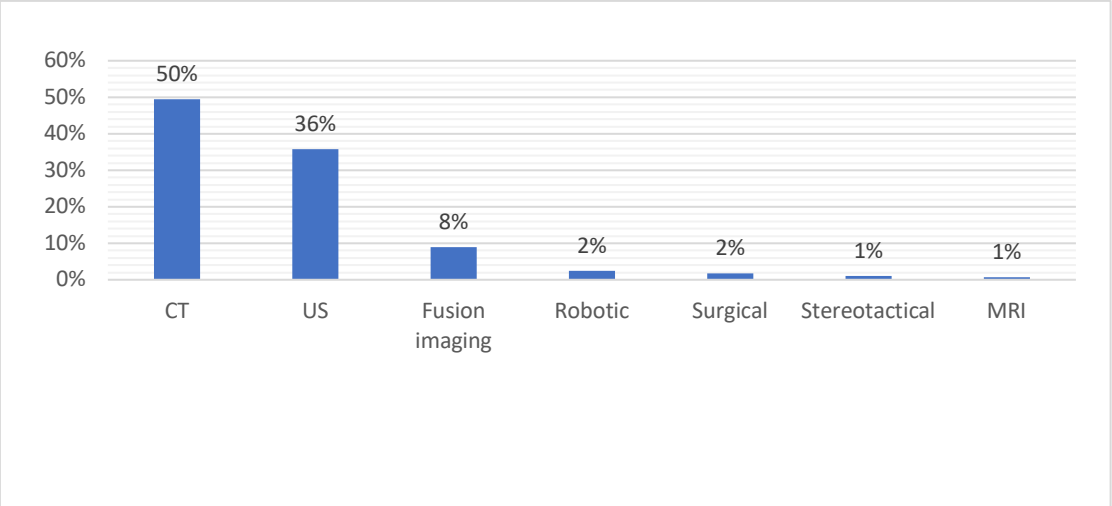


Figure 9: Guidance methods in performing MWA

3.4.2 Ablation method

A greater number of all MWA was done with a percutaneous approach, namely 90% of the patients. Laparoscopic approach MWA had only 4% of the patients, and surgical or open approach MWA had 6%.

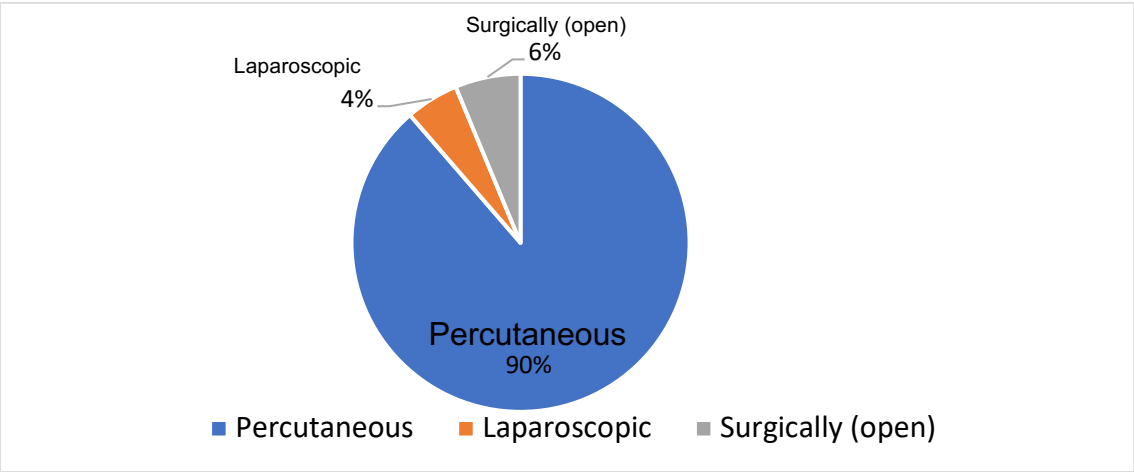


Figure 10: Ablation methods in performing MWA

3.4.3 Technical parameters of MWA per lesion

The cumulative ablation median time per lesion was 8 minutes, and the median ablation power used per lesion measured 100 Watts. The median number of probe placements per lesion was 1 probe.

All sites reported 99% of technical success after the performed treatments.

3.4.4 MWA procedural medication

Most of the patients, 47%, received general anaesthesia with intubation, while only 1 % received general anaesthesia with jet ventilation. Deep sedation with Propofol was used in 18% of the patients. 29% of the patients were treated periinterventionally with Fentanyl / Midazolam or similar drugs.
Data is missing for 5% of the patients.

3.4.5 Hospitalization

The median number of overnight stays at the hospital is 1 night.
More than half of the patients - 52% had only 1 day of hospitalisation. Another 24% spent 2 nights in hospital and 9% of the patient were treated ambulant with no night spent in hospital. 12 % of the patients had 3 or more days of hospitalization. The maximum hospitalisation was 19 days.

3.4.6 Adverse events (AEs)

3.4.6.1 Acute AEs

A total of 117 acute AEs, grading from Grades 1 to 4, were reported. No Grade 5 acute AEs were reported. All acute AEs occurred within 30 days after MWA. Two acute AEs are missing.

Table 1: Acute AEs after MWA

Acute AEs		
	AEs	Patients n (%)
Grade 1	55	40 (8)
Grade 2	32	29 (6)
Grade 3	24	21 (4)
Grade 4	6	6 (1)
Grade 5	0	0
Related		
Yes	95	66 (13)
No	24	16 (3)
Related serious		
Yes	21	19 (4)
No	8	9 (2)

3.4.6.2 Related and Likely Related Acute AEs

Pain is the main acute AE reported, consisting of 18 Grade 1-AEs, 2 Grade 2-AEs and 1 Grade 3-AEs. Haemorrhage was reported in 12 acute AEs. 4 Grade 1-AEs, 6 Grade 2-AEs, 1 Grade 3- and 1 Grade 4-AEs. Nausea was reported in 5 acute AEs. 3 of them were Grade 1-and 2 Grad 2-AEs. Vomiting was reported in 3 acute AEs. 2 Grade 1-AEs and 1 Grade 2 AE. Liver abscess was reported in 6 acute AEs. 1 Grade 2-AEs, 5 Grade 3-AEs. Subcapsular hematoma was described in 5 acute AEs. 4 Grade 1- and 1 Grade 4- AEs. Asthenia were reported in 2 acute AEs, 1 Grade 1- and 1 Grade 2- AEs. Hypertonia was reported in 3 acute AEs, of which 1 Grade 1-, 1 Grade 2- and 1 Grade 3-AEs. Portal vein thrombosis was described in 3 acute AEs. 2 AEs were Grade 2, and 1 AEs was Grade 3. Fever was reported in 5 acute AEs. 3 Grade 1-, 1 Grade 2- and 1 Grade 3-AEs. Pneumothorax was reported in 2 acute AEs. 1- Grade 2 and 1- Grade 3-AEs. Pleural effusion needing drainage was reported in 1 acute Grade 2- AEs. Pleural fluid was described in 1 acute Grad 1-AEs. Biliary leakage/fistula or

occlusion was described in 1 Grade 3-AEs. Ascites was reported in 2 acute AEs. 1 Grade 1 and 1 Grade 2-AEs. Sepsis was described in 2 acute AEs, both of them Grade 3-AEs. Hyperbilirubinemia was also reported in 1 acute AE, Grade-2. Urinary tract infection was reported in 1 acute Grade 2-AE. Post ablations syndrome was seen in 1 acute Grad 1-AE.

43 other related and likely related AEs are not differentiated.

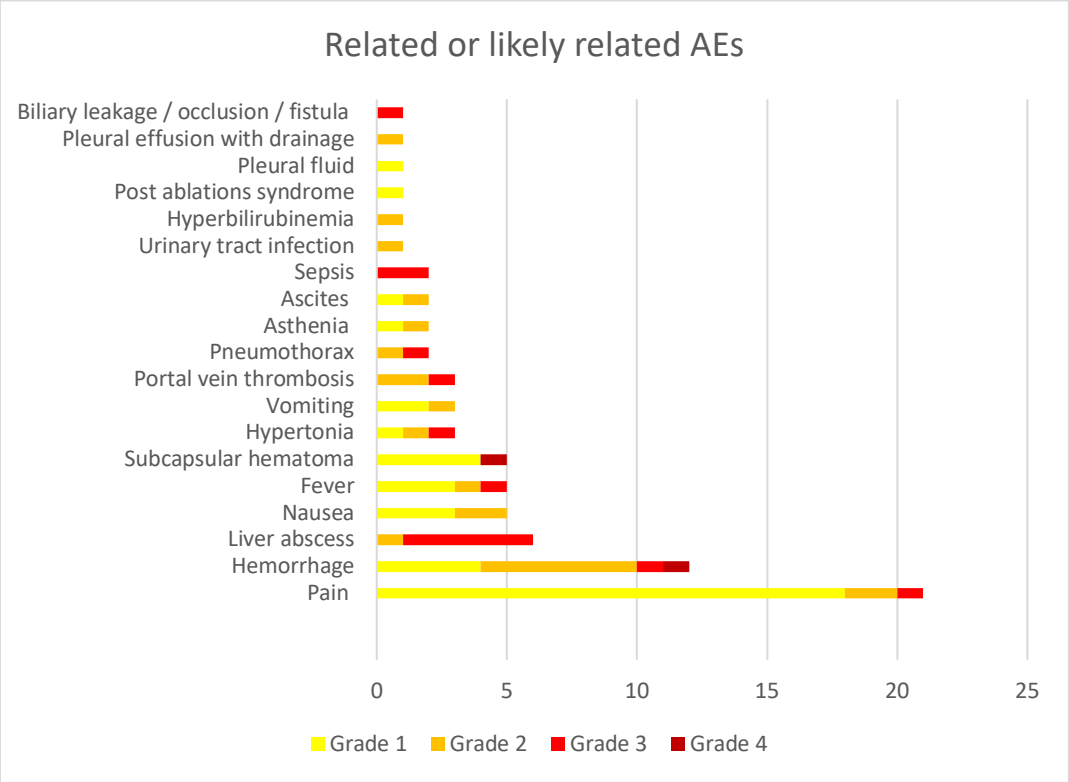


Figure 11: Related or likely related acute AEs after MWA

3.4.6.3 Chronic AEs

All chronic AEs occurred in more than 30 days after MWA. Out of 7 Grade 5 AEs, only one is likely to be related due to biliary leakage/occlusion / fistula.

Table 2: Chronic AEs after MWA

Chronic AEs		
	AEs	Patients n (%)
Grade 1	9	6 (1)
Grade 2	15	13 (3)
Grade 3	30	20 (4)
Grade 4	10	7 (1,4)
Grade 5	7	7 (1,4)
Related		
Yes	14	12 (2,4)
No	57	29 (6)
Related serious		
Yes	7	5 (1)
No	33	19 (4)

3.5 Quality of life data

Out of 500 patients, only 186 QoL questionnaires at Baseline and Follow-up 1 were filled out.

3.5.1 Global health score

According to the global health score (p = 0,019), 68 % of the patients were stable or improved global health from Baseline to Follow-up 1. 32% decreased global health.

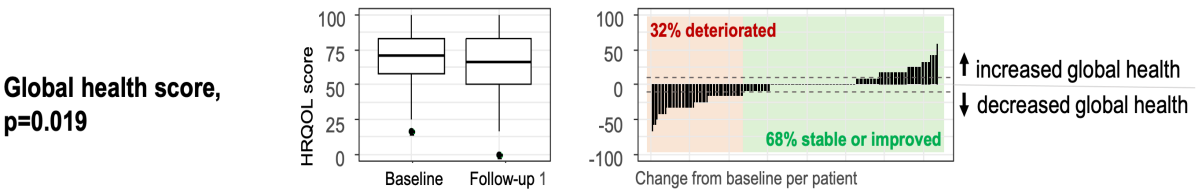


Figure 12: Global health score from Baseline to Follow-up 1

3.5.2 Function score

Concerning function score (p = 0,197), only 22 % of the patients decreased in functioning, and 78% were stable or improved.

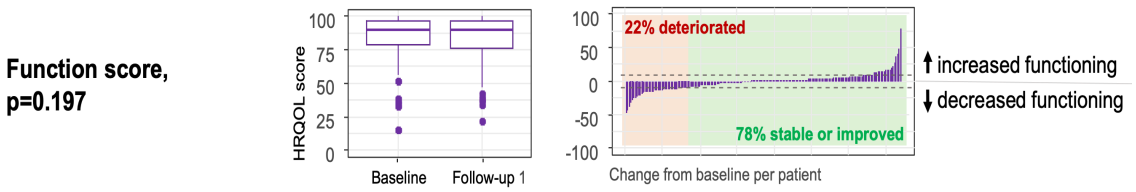
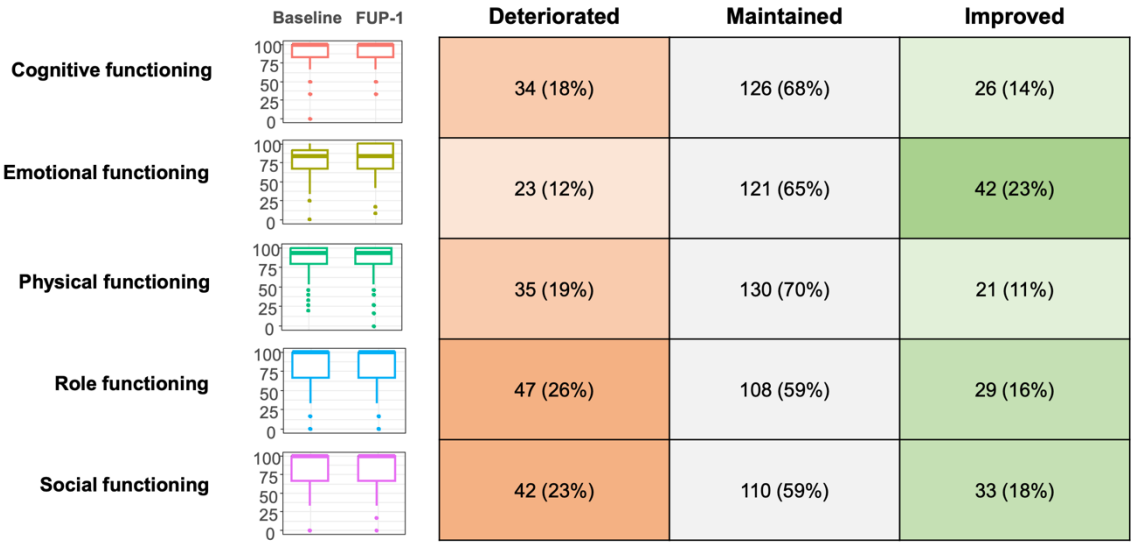


Figure 13: Function score from Baseline to Follow-up 1

No significant differences were monitored in the function score breakdown between cognitive, emotional, physical, role and social functioning.



	Deteriorated	Maintained	Improved
Cognitive functioning	34 (18%)	126 (68%)	26 (14%)
Emotional functioning	23 (12%)	121 (65%)	42 (23%)
Physical functioning	35 (19%)	130 (70%)	21 (11%)
Role functioning	47 (26%)	108 (59%)	29 (16%)
Social functioning	42 (23%)	110 (59%)	33 (18%)

Figure 14: Breakdown of the function score from Baseline to Follow-up 1

Missing data for 2 patients concerning role functioning and for 1 patient concerning social functioning.

3.5.3 Symptom score

Stable or improved symptom score (p = 0,001) showed 84 % of the patients, and only 16% deteriorated from Baseline to Follow-Up 1.

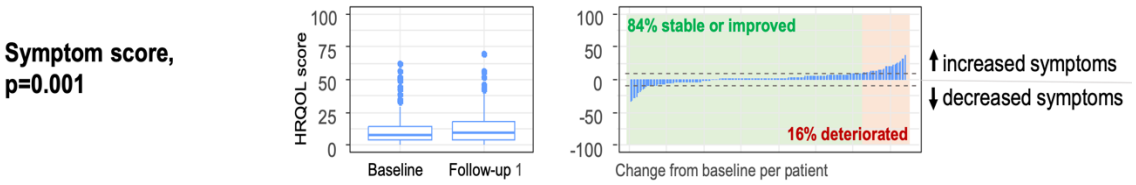


Figure 15: Symptom score from Baseline to Follow-up 1

Increased symptoms were shown, including fatigue, pain, and shortness of breath.

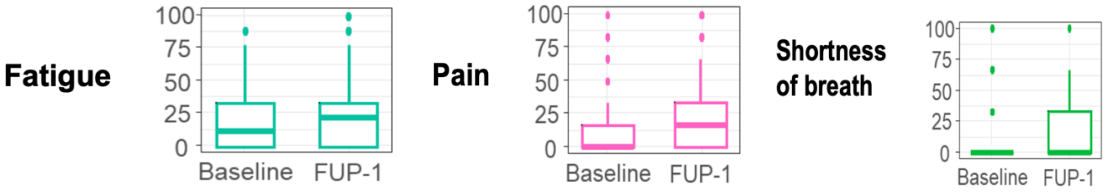


Figure 16: Fatigue, Pain, and shortness of breath as symptoms from Baseline to Follow-up 1

No differences were reported concerning appetite loss, constipation, diarrhoea, insomnia, nausea, or vomiting.

4. Discussion

CRC has a high incidence; over time, approximately 40 to 50% of CRC patients will develop CRLM. Currently, the first treatment option for CRLM is surgical resection, where the 5-year survival rates can reach 30 to 40%, but only 20 % of CRLM patients can be entirely cured (de Haas *et al.*, 2011b). With the evolution of chemotherapy and new target agents, the survival rates in Patients with unresectable CRLM drastically enhanced from 8 – 10 months to 20 – 24 months, and some patients with CRLM that primarily were not suitable for resection have become operable with curative intent (Leonard, Brenner and Kemeny, 2005; Kemeny, 2006).

In recent years, minimally invasive treatments such as RFA or MWA have also developed into an established therapy option for smaller unresectable CRLM and as a therapy option for patients not suitable for surgery. Further, MWA is also increasingly used in a curative manner (Cervantes *et al.*, 2023).

To define which patients can benefit from MWA, real-world data are needed. Yet, IR is facing many challenges in obtaining such data. While RCTs are considered the gold standard for assessing treatment efficacy, their applicability and reliability in IR may be limited due to challenges in blinding, randomization, inadequate sample recruitment, and size (Wang and Kohi, 2018). In the rapidly evolving field of IR, RCTs may not always be feasible to implement quickly and with sufficient quality. For example, in the field of vascular- and IR only 117 RCTs were published between 1995 and 2014, of those, 52,2 % were recognized to be in poor quality (Hong *et al.*, 2016). Further, the well-known limitations of traditional RCTs - such as restrictive patient and provider selection, high costs, and limited scope of evaluable interventions - have prompted the exploration of alternative methods and settings for conducting these studies (Choudhry, 2017).

In this set of circumstances, observational studies, pragmatic trials and in particular real-world data in form of registry studies may play a complementary and important role in answering many of the clinical questions in IR (Wang and Kohi, 2018).

RCTs and observational studies are often viewed as opposing research methods. However, comparing these methods on the same clinical questions showed that observational studies did not overestimate treatment effects compared to RCTs (Ioannidis, 2001). Ioannidis JPA et al. looked for causalities in two reports comparing observational studies and RCTs in diverse treatments. Both reports showed a high concordance between the results of the two designs, with a correlation coefficient of 0.84. Observational studies displayed similar odds ratios among themselves, while RCT results varied more, suggesting that observational studies might sometimes offer more consistent results (Ioannidis, 2001).
In another study comparing the results of non RCTs and RCTs that evaluated medical interventions, Ioannidis JPA et al. identified 45 topics where both RCTs (n=240) and non RCTs (n=168) had been conducted and included in meta-analyses of binary outcomes. A strong correlation was found between the summary odds ratios of both RCTs and non RCTs studies, with a coefficient of 0.75 ($p < .001$) (Ioannidis *et al.*, 2001).

The concept of pragmatism in clinical trials arose due to the concern that numerous trials were not adequately guiding clinical practice. These trials frequently focused on determining efficacy, involved relatively small sample sizes, took place at sites with seasoned investigators, and included participants who were highly selected (Schwartz and Lellouch, 1967). This resulted in the recognition that there was a need for more pragmatic trials to show the real-world effectiveness of interventions in diverse patient populations. Pragmatic trials typically involve complex interventions with various interacting components and often necessitate the skills and expertise of multiple healthcare professionals to administer the intervention (Ford and Norrie, 2016).
Price et al. conducted two analogous pragmatic trials to evaluate the real-world effectiveness of leukotriene-receptor antagonist (LTRA) with both a long-acting beta 2-agonist (LABA) or an inhaled glucocorticoid for first-line asthma-controller therapy as an addition therapy in patients who already undergo with inhaled glucocorticoid therapy. After only two months, the study's findings indicated that LTRA showed similar effectiveness to an inhaled glucocorticoid as first-line

therapy and to LABA as an add-on therapy for many primary care patients. This Equivalence was not proved at 2 years. A major limitation was nonadherence to the prescribed regimen (Price *et al.*, 2011).

The use of RWD to generate real-world evidence, alongside interventional clinical trial-based research, is rapidly increasing, in particular with using medical registry studies. The distinction between RWD and data from randomized clinical trials lies in the method of data collection, as per definition RWD are obtained directly at the point of care (Kokkotou *et al.*, 2024). Registry studies use structured system that employs observational techniques to gather consistent RWD for assessing specific outcomes within a given population. Moreover, by developing a comprehensive database of clinical outcomes through a registry, the generalizability to a broader target population can be improved by including a more diverse range of ages, ethnicities, and comorbidities. Additionally, registry studies can serve multiple purposes in providing real-world data (RWD), particularly in describing the natural history of a disease, measuring or monitoring safety and adverse effects, and assessing the clinical and cost-effectiveness of healthcare services. (Gliklich et al., 2014). Another advantage of participating in registry studies is the opportunity to compare outcomes with regional and national benchmarks, resulting in stronger quality control and improved patient care. (Uberoi *et al.*, 2012; Dykes, Bhargavan-Chatfield and Dyer, 2015).
Using prospective, active surveillance of a clinical registry swiftly (within 12 months) possible safety alerts were identified in patients who received Mynx vascular-closure device after percutaneous coronary intervention with femoral access in one study from Resnic et al. This study reported a significantly greater risk of access-site bleeding and transfusion, compared to alternative vascular-closure devices in 48992 patients from the analysed 73124 patients (Resnic *et al.*, 2017).

However, when a therapy response cannot be accurately measured due to disease characteristics, or when there is a need to estimate a comparative treatment effect within the population of interest, other methods have been

developed to supplement the data with data from outside the clinical trial, known as an external control arm. External control arm can be obtained from previous clinical trial data (pooled or individual) or from observational RWD, including registries, electronic health records, and medical or pharmacy claims. (Mishra-Kalyani *et al.*, 2022).
For instance, using external control arm gained from RWD from the ARROW trial, evidence supporting pralsetinib as a more effective first-line treatment option for RET fusion-positive advanced non-small cell lung cancer (aNSCLC) compared to pembrolizumab alone or pembrolizumab combined with chemotherapy was demonstrated (Popat *et al.*, 2022).

Overall, the goal of real-world data derived from registry studies in IR is to complement evidence from traditional clinical trials and provide a comprehensive understanding of how IR interventions perform in real-world clinical practice.
At present, to the best of our knowledge, CIEMAR stands as the world's first prospective registry study for MWA in CRLM.

4.1 Patient characteristics

Most of the patients involved in this study showed ordinary daily activity and could perform all pre-disease activities without restriction or had a slightly decreased physical activity but were able to carry out light work. Only a tiny amount of the patients who presented an ECOG score from 2 to 4 were disabled or with limited self-care, confined to a sedentary lifestyle with more than 50% of the total. Many clinical trials for patients with CRLM tried to prove a relationship between a lower ECOG score and a better disease outcome. One big study involving 3143 patients who underwent a first-line 5-FU chemotherapy showed that patients with an ECOG score of 0 compared with an ECOG score of 1 have a decreased probability of fatal or serious AEs, high-grade anaemia, and high-grade nausea. Further, the patients with an ECOG score of 0 had better progression-free survival and overall survival, where the median overall survival was 27,63 months versus 20 months in the patients with an ECOG score of 1 (Abdel-Rahman, 2019). Higher ECOG scores than 1 are linked with increased comorbidities, which can

eventually play an essential role in the treatment outcome using any treatment modality.

Although the majority of the patients were fully active, nearly 74% of the patients showed a higher clinical risk score - FONG score, making them probably not suitable for surgical resection of CRLM. According to the FONG score, based on three oncological parameters (CEA, disease-free interval, node-positive primary tumour) and two imaging factors (size and number of CRLM) (Fong *et al.*, 1999), the therapy for the patients with scores from 3 and 4 should be reconsidered, and surgery should be delayed. Patients with moderate and high FONG scores can primarily benefit from more aggressive systemic and locoregional interventional oncological therapies.

Li Destri et al. noted that the resectability rate drops together with the rising of the FONG score, where the rate of resectability for score 0 was 100%, score 1, 76,9%, and score 3, 66%, respectively. Additionally, this study pointed out that CEA results above 200 ng/ml shall raise the alarm considering resection of CRLM (Li Destri *et al.*, 2008). Further, they tried to evaluate the percentage of unnecessary laparotomy in the case of understaged patients with lower FONG scores using diagnostic laparoscopy and US. In fact, patients with higher FONG scores would have a higher percentage of spared unnecessary laparotomies, where FONG score 0 and 1 would have saved 12% of unnecessary operations, and patients with FONG scores of 2 to 3, 38% of unnecessary operations (Li Destri *et al.*, 2008).

Predicting mortality using CCI based on 16 comorbid conditions showed that nearly 20% of our patients have severe comorbidity presenting a CCI from 5 to 17, and 37% of the patients presented CCI from 3 to 4. The 1-year mortality rate for a CCI of ≥ 5 equals 85%, and for a CCI of 3-4, 52% (Charlson *et al.*, 1987).

In resectable CRLM, patients with low CCI proved to have the highest survival, and patients with higher CCI showed a higher risk of death (Nassabein *et al.*, 2021).

Although liver resection is still the ‘golden standard’ for the therapy of CRLM, most patients are not surgical candidates due to known comorbidities together

with extrahepatic disease or high tumour burden of the liver (Jarnagin *et al.*, 2002; Poon *et al.*, 2004).
A high consensus was reached for thermal ablation over partial hepatectomy as an alternative therapy option in patients with deficient general health status with CCI 5-8, ECOG 2, and ASA 3 (American Society of Anaesthesiology) in the multidisciplinary consensus document from the COLLISION trial group (Nieuwenhuizen *et al.*, 2020).

In our study, only 37,2 % of patients fully completed the QoL questionnaire at both Baseline and Follow-up 1. Among these patients, 68% reported stable or increased global health, while 32% reported a decrease in global health, which was statistically significant (p=0,019). 78% of the patients were stable or improved in terms of function score, and only 22% of the patients decreased in functioning. No statistical significance was shown in the function score breakdown. Statistical significance was observed in the symptom score (p=0,001), indicating that 84% of the patients either remained stable or showed improvement at follow-up 1. Conversely, only 16% of the patients experienced deterioration, exhibiting increased pain, fatigue or shortness of breath.

When considering therapy of CRLM, calculating the ECOG and FONG scores as well as CCI can help us screen patients, where increased scores can indicate an impaired health status, which often can be a predictor of poor therapy outcome. In such cases and in patients unfitting for surgery, therapy with MWA should be reconsidered. The real-world data for QoL suggest that the majority of the patients showed stability or improvement in global health, functioning, and symptoms over time.

4.2. Tumour characteristics

Regarding the primary tumour, most patients presented CRC in the left colon, the rectum, and the right colon. Corresponding to the widely accepted ‘’anatomical/mechanical’’ and ‘’seed-and-soil’’ hypotheses in explaining metastatic spread (Viadana, Bross and Pickren, 1978; Weiss *et al.*, 1986; Langley

and Fidler, 2011), the location of the primary CRC plays an important role in spreading distant metastases and their patterns. 65 % of our patients who presented with a primary tumour in the colon had CRLM, which can be explained by knowing that blood from the colon and proximal part of the rectum is drained through the V. portae in the liver. The distal parts of the rectum spread metastases primarily in the lungs by surpassing the drainage system through the V. portae. In our case, only 59 patients had lung metastasis, and 58% of them had only one or two metastases.

Studying patterns of distant metastasis of CRC from several nationwide registers in Sweden involving 9364 patients with metastases from CC and 5601 patients with metastases from RC showed that the most frequent sites of metastatic spread were the liver (70 % in CC and 70% in RC) and the thorax (32 % in CC / 47 % in RC) (Riihimäki *et al.*, 2016b).

The location of the metastases and the tumour stadium revealed a crucial part in the survival of patients with CRC; namely, the median survival of patients with CRLM was 9 months, and for those with lung metastases, 14 months. The T and N stages firmly impacted survival, reviling 16,5 months for T2-stage and 8 months for T4-stage, 19 months for N0-stage compared to 8 months for N2-stage (Riihimäki *et al.*, 2016b). The location of the primary tumour was shown to play also a role in OS after hepatic resection of CRLM in a big meta-analysis of 12 different studies, including 6387 patients. Right-sided primary tumours display significantly poor 5-year OS rates with a hazard ratio (HR) of 1,354, contrary to the primary left-sided CRC showing an HR of 1,104 after hepatic resection (Liu *et al.*, 2019).

The prognostic factors in CRC can be explained based on their embryological origin because the left colon develops from the hindgut and the right colon from the midgut. CRC from these regions have also shown differences regarding mutations and microsatellite instability and are seen as different clinicopathological entities (Benedix *et al.*, 2012).

Concerning mutations and microsatellite instability, some data in our study are missing mainly because different sites have different working protocols or data from patients' histories were not available. Nevertheless, the available data

shows that most of the lesions had RAS or Kirsten rat sarcoma virus (KRAS) mutations.

One retrospective study, including 136 patients with 218 ablated colon liver metastasis (CLM), studied the effects of the ablation margins on the local tumour progression-free survival (LTPFS). Calandri et al. pointed out that ablated CLM with ablation margins ≤ 10 mm had significantly worse 3-year LTPFS rates than the ablated lesions with ablation margins ≥ 10 mm in both mutant RAS and wild-type RAS mutation (Calandri *et al.*, 2018). The lesion mutation can be helpful in planning MWA regarding the size of the ablation zone, which can have a greater meaning in RAS-mutated lesions. Mutant RAS in CRLM is associated not only with an elevated rate of local tumour progression but also with an earlier onset after percutaneous ablation (Odisio *et al.*, 2017). Based on the Amsterdam Colorectal Liver Met Registry (AmCORE), a higher probability of death and relapse was reported in CRLM with BRAF mutation as well as in lesions with MS instability if they didn't undergo an immunotherapy (Dijkstra, Nieuwenhuizen, Puijk, Florentine E. F. Timmer, *et al.*, 2021). To obtain local control in lesions with KRAS mutation, Shady et al. proposed safety ablation margins of > 6 mm since margins of 1 – 5 mm after thermal ablation pointed to higher local tumour progression rates, showing that KRAS mutation is also an important predictor of LTPFS (Shady *et al.*, 2017).

Relating to complication rates after ablation, Dijkstra et al. pointed out that lesions with RAS mutation had a complication rate of 24,6 % and 25% for RAS-wild-type. No significant dissimilarity in complication rates was seen in KRAS-mutation or MSI (Dijkstra, Nieuwenhuizen, Puijk, Florentine E. F. Timmer, *et al.*, 2021).

In general, MWA and other ablative methods hold to be a therapy option for candidates unsuitable for surgical resection. However, in the last two decades, equivalent clinical outcomes have been presented comparing thermal ablation and surgery in CRLM smaller than 3 cm. In our study, the median size of the lesions was 1,5 cm, where all sites reported 99% technical success after MWA. Comparing repeated thermal ablation and repeated partial hepatectomy in CRLM from 0 to 3 cm, no statistically evident dissimilarity regarding LTPFS, overall

survival (OS), or distant progression-free survival (DPFS) was proven in 136 patients, where the median size of the lesions in the partial hepatectomy group was 21 mm and 16,5 mm in the ablation group (Dijkstra, Nieuwenhuizen, Puijk, Florentine E.F. Timmer, *et al.*, 2021). In another study examining the efficacy of thermal ablation of small-size CRLM from 0 to 3 cm versus CRLM from 3 to 5 cm (intermediate-size) in a total of 338 patients, differences in median OS, L, TPFS, and local control (LC) were pointed. The median OS for the small group metastasis was 53,0 months, and for the intermediate-size group, 40,7 months. Regarding LTPFS, superior results were shown in the small-size group showing 1-, 3- and 5-year LTPFS rates of 92,5 %, 88,1 %, and 88,1 %, respectively, versus 74, 7%, 66,0%, and 66,0% respectively in the intermediate-size group. Better rates were revealed concerning LC too, for the small-size group 1-, 3- and 5-year rates were 98,6%, 96,7%, and 94%, respectively, superiorly to 93,9%, 85,4%, and 81,5%, for the intermediate-size group (Dijkstra *et al.*, 2023). In the multidisciplinary consensus document from the COLLISION trial group, a strong consensus for thermal ablation as an appropriate treatment was pointed for small-size and resectable CRLM sitting deep in the liver parenchyma requiring major hepatectomy. Further, unresectable CRLM sizing $\leq$ 3 cm should undergo a thermal ablation as well as unresectable CRLM sizing 3 – 5 cm when system therapy for further downsizing is problematical (Nieuwenhuizen *et al.*, 2020).

Moreover, using a concomitant MWA therapy with surgical resection may spare a two-stage hepatectomy in patients with CRLM. Philips et al. described that combining MWA with single-stage hepatectomy gave a similar outcome compared with two-stage hepatectomy. The OS for single-stage hepatectomy + MWA was 38,4 months vs 42,2 months for two-stage hepatectomy. Additionally, in bilobar CRLM, less overall morbidity was reported (Philips *et al.*, 2016). Bilobar CRLM is still a challenge for both hepatectomy and ablation therapy. Examining outcome after combined resection and MWA versus hepatic resection alone in bilobar CRLM showed no significant differences in hepatic recurrence-free survival, OS, and disease-free survival (Tanaka *et al.*, 2006). The new prospective multicentre trial on survival after stereotactic MWA (SMWA) vs hepatectomy for resectable CRLM - MAVERRIC announced an actual 3-years

OS rate of 78% after SMWA versus 76% in hepatectomy, and the estimated 5-years OS rate were 56 % after SMWA versus 58% after hepatectomy (Tinguely *et al.*, 2023). In this study, the median tumour size was 16 mm in the SMWA cohort and 18,5 mm in the matched hepatectomy cohort.
New data for ablative treatments as an alternative to hepatectomy are awaited in the currently ongoing studies COLLISION trial NCT03088150, HELARC trial NCT02886104, and NEW-COMET trial NCT05129787.

As already mentioned, the location of the CRLM in the liver parenchyma, including deep seeded lesions and lesions adjacent to critical structures, can play a demanding role in treatment with surgical excision. Ablative techniques can offer an alternative therapy in awkwardly placed CRLM adjacent to large vessels or biliary structures. The location adjacent to critical structures in our study showed 215 lesions. Of them, roughly 50% or 113 lesions were seated adjacent to large vascular structures, and 12 lesions showed proximity to bile structures, along with 57 lesions adjacent to the diaphragm.
In order to achieve tumour destruction, thermal ablative methods relied on producing heat in the target tissue. However, the circulating blood in the large vessels during an MWA can sink the desired temperatures, creating a 'heat sink effect', which, on the other hand, can compromise its effectiveness, consequently elevating the risk of local recurrence (Rhaiem *et al.*, 2020). Unlike RFA, MWA is not affected by charring at the probe tip due to active heating, producing a more extensive and more uniform ablation zone (Gravante *et al.*, 2008). Using microscopic examination of MWA zones, clear coagulation necrosis was reported near large vessels bigger than 3 mm in diameter (Simon, Dupuy, and Mayo-Smith, 2005). Dodd et al. performed RFA and MWA in bovine liver models, which were blood perfused, assessing the effects of portal venous blood flow on the ablation zone. 60 ex vivo ablations in 15 liver models were performed with portal vein blood flow at 60 – 100 ml/min/100g. The size of the ablation zone was not affected by changes in blood flow (Dodd *et al.*, 2013). Ringe et al. tried to quantify the heat sink effect in ex vivo models using MWA and the influence of the antenna-vessel distance, reporting that no notable impact on the morphology of the

ablation zone due to vessel perfusion in an antenna-vessel distance of 20 mm (Ringe *et al.*, 2015). The impact of hepatic vein size on the heat sink effect was monitored in porcine models by doing MWA near small ≤ 3mm, medium 3-6mm, and large ≥ 6 hepatic veins outlining no distortion of the ablation zone and extending to the entire circumference of the vessel (Yu *et al.*, 2008). Several procedures have been proposed to overcome the heat sink effect, ranging from short-term balloon occlusion of a particular hepatic vessel, arterial embolisation, and use of chemoembolisation to decreasing blood flow with pharmaceutics as well as using the Pringle manoeuvre where executing an ablative method at laparotomy (Ahmed *et al.*, 2011b).

Producing excessive heat to prevail over the heat sink effect can induce severe damage to the near major bile ducts, resulting in bile leak, bilioma development, or bile stenosis. Lesions near the gallbladder can also be demanding for ablation because of gallbladder perforation or producing thermal cholecystitis. Even though complications of the gallbladder are hardly life-threatening, they can be a source of reduced quality of life (Ozen and Raissi, 2022). Comparing MWA to RFA, lower rates of biliary complications are reported (Mann *et al.*, 2010).

Subdiaphragmatic seated liver tumours can be challenging to target due to the different positions of the target lesion during the breathing cycle. In the management of these lesions, there are mainly two concerns in the course of MWA: unsuccessful ablation, which gives local tumour progression, or requiring transpleural access. In one large retrospective study, Chieu et al. outlined that transpleural access is a safe way of treating subdiaphragmatic lesions, describing minor complications and reporting that pneumothorax was the most common complication (Vo Chieu *et al.*, 2018).

4.3 Safety of MWA

Thermoablative techniques are generally considered to be relatively safe and less invasive in any used approach compared to hepatectomy. Morbidity and mortality rates after ablative therapy reported in the literature range between 4 % and 9 % morbidity (Mulier *et al.*, 2002; Wong *et al.*, 2010; Birsen *et al.*, 2014;

Groeschl *et al.*, 2014; Gillams *et al.*, 2015) and approximately 0 – 2% mortality (Mulier *et al.*, 2002; Wong *et al.*, 2010; Gillams *et al.*, 2015).

In the current study, all AEs were divided into acute and chronic according to CTCAE Version 5.0, where an acute AE was between 30 days from MWA. The majority of the related or likely related acute AEs were minor, seen in 13% of the patients. Major serious related acute AEs were reported in 3,8% of the patients. No acute Grade 5 AEs were reported. The most common related or likely related acute AEs was pain (n – 21), and the second common acute AE was haemorrhage (n – 12), where only two AEs were considered major complications. Liver abscess (n - 6) is the third most common acute AE, with 5 major complications and one minor. Most of the other related and likely related acute AEs were minor complications. Other major acute complications were subcapsular hematoma (n-1), fever (n-1), hypertonia (n-1), pneumothorax (n-1), sepsis (n-2), and biliary complications (n-1).
In the chronic AEs group, 71 were reported, of which only 14 were related in 2,4% of the patients. 7 serious related chronic AEs were seen in 1 % of the patients. One chronic Grade 5 AE was seen due to biliary complication; the other six reported Grade 5 AEs were not related.
There was 99% technical success in all performed MWA, where the median number of MWA antenna placement was 1 probe per lesion basis.

In one retrospective study, 102 CRLM with a mean tumour size of 1,8 cm underwent MWA. The major complication rate was 4%, and the overall complication rate was 8%. The three major related complications reported were bile leak with building an abscess fixed with drainage, pulmonary embolism treated with anti-coagulation, and tract seeding in one patient, which underwent a biopsy in an almost identical trajectory. Minor complications involved body wall arterial bleeding and asymptomatic pneumothorax. No deaths were reported within 30 days after MWA (Knott *et al.*, 2021). Livraghi et al. conducted one extensive study concerning complications in MWA for liver tumours, including 736 patients with 1037 lesions. 522 of the patients had hepatocellular carcinoma

(HCC), 187 of the patients had liver metastases, mostly CRLM, and 27 had cholangiocellular carcinoma (CCC). The size of the lesions extended from 0,5 cm to 10 cm. Reported major complications had only 2,9% of the patients or 22 patients, where the main complications were symptomatic pleural effusion, bowel perforation, intraperitoneal bleeding, and liver decompensation. Out of these 22 patients, 6 major complications occurred in patients with liver metastases and 16 in patients with HCC. Minor complications had 7,3 % of the patients, where the most common complication was asymptomatic pleural effusion, followed by liver decompensation and subcapsular hematoma. No mortality was described (Livraghi *et al.*, 2012).

Describing complications in treatment with percutaneous MWA in a cohort of 1136 patients, Liang et al. did a total of 3697 MWA sessions in the therapy of 1928 malignant liver lesions. Major complications took place in 30 patients, or 2,6%, counting liver abscess and empyema, tumour seeding, perforation of the colon, bile duct injury, pleural effusion with a mandatory thoracentesis, haemorrhage with the need for arterial embolisation and skin burn. Minor complications included pain, gallbladder wall thickening, fever, small stricture of the bile duct, asymptomatic pleural effusion, and arterioportal shunt. Further, an increased number of major complications were associated with the usage of a noncooled-shaft antenna with parallelly elevated ablation sessions (Liang *et al.*, 2009). When comparing complications using SMWA or open or laparoscopic hepatectomy in the prospective MAVERRIC trial, significant differences were presented. 10 % of the SMWA cohort had complications within 30 days of follow-up versus 30 % in the hepatectomy cohort. Major complications were described only in 2% of the SMWA cohort, and 10% of major complications were reported in the hepatectomy cohort. In the SMWA, two major complications were described, haematothorax requiring pleural drainage and one death in a patient with a liver abscess with gastrointestinal fistula; this patient died due to a cardiac event following surgical reintervention (Tinguely *et al.*, 2023). Takahashi et al. revealed a 90-day morbidity of 7% in a prospective study of 87 open and 13 laparoscopically MWAs after excluding patients with concomitant liver and CRC resection. The main complications described in one patient each were acute

kidney injury, portal vein and superior mesenteric vein thrombosis, thrombosis of the internal jugular vein with pulmonary embolism, exacerbation of chronic obstructive pulmonary disease, and postoperative pneumonia. One unrelated mortality was reported due to gastrointestinal bleeding one month after laparoscopically done MWA (Takahashi, Kahramangil, and Berber, 2018).
Regarding complications and CRLM size, two groups were analysed in the AmCORE study, and no significant differences were found in the severity or number of complications between the small-size group and the intermediate-size CRLM group. 14,9 % or 33/221 patients had complications in the small-size group versus 15,3% or 9/59 in the intermediate-size group. Only one patient had a Grade 4 complication in the intermediate-size CRLM group, presenting with post-procedural ileus following aspiration pneumonia. The median hospitalisation reported was 1 day in the small-size CRLM group versus 4 days in the intermediate-size group (Dijkstra *et al.*, 2023).

In the present study, 85% of the patients were hospitalised for 2 days, while 52% had only one overnight stay. Only 12 % were hospitalised for 3 or more days. The median number of hospitalisations is 1 day.
Song et al. showed slightly increased results for hospitalisation after MWA, mean duration of hospitalisation was 5,9 $\pm$ 0,9 days. In the same study, hospitalisation after hepatic CRLM resection was significantly higher, with a mean hospitalisation of 11,8 $\pm$ 6,9 days (Song *et al.*, 2017). Compering hospitalisation in 4639 patients who underwent surgical resection versus combined resection and ablation of CRLM, lower hospital stay was reported in the combined resection and ablation group with median hospitalisation of 6 days versus 7 days in the resection group (Elfrink *et al.*, 2021). In a 10-year analysis from the AmCORE study, the mean length of hospitalisation for open ablations was 6,9 days, and the mean hospitalisation after percutaneous thermal ablation was 1,4 days (Puijk *et al.*, 2022).
In our case, 90% of the ablations were done with a percutaneous approach. The other 10% of the lesions were ablated either laparoscopically 4% or surgically 6%.

Concerning complications and hospitalisations related to thermoablative therapies, comparing the results mentioned earlier with the results of our study, the rate of complications and hospitalisation is significantly lower after thermoablation versus surgical resection of liver tumour lesions, especially done by a percutaneous approach.

Several guidance methods for performing percutaneous MWA are used to improve clinical benefits and reduce complications. CT and US are still the most frequently used image guidance methods (Hao *et al.*, 2022).
Likewise, we found that most of the lesions in our study underwent CT—or US-guided percutaneous MWA; namely, 50% of the lesions had CT-guided and 36% US-guided ablation. One small part of the lesions was ablated using real-time fusion imaging, covering 8% of the lesions. MR guidance was used in only 1% of the CRLM, as well as stereotactic MWA guidance.
The benefits of using CT-guidance are sustained in its availability, lowered operator dependence, and rapid assessment of the residual tumour and ablation margin (Lin *et al.*, 2021). The main advantage of US-guidance is the ability to provide real-time monitoring of MW antenna placement without using ionising radiation, contrary to using CT-guidance (Lin *et al.*, 2021). Fusing some of the guidance methods can combine the strength of the modalities and can improve outcomes in the very small hepatic lesion. Mauri et al. used real-time virtual navigation with US-CT or US-MRI in 295 small liver tumours (133 metastases and 162 HCCs) that were detectable at baseline with CT or MRI but undetectable using conventional US. Assessing the ablation zone after 24 hours using CT or MRI showed that 95,6% of the tumours were correctly targeted, providing a 0,5 – 1,0 cm ablative margin in healthy liver tissue for 90,2% of the tumours (Mauri *et al.*, 2015).

5. Summary

In summary, this RWD study from a prospective registry study aligns with numerous clinical studies over recent decades, reporting that MWA is a valuable therapeutic option in selected patients with CRLM or for those who are not candidates for surgery. MWA demonstrates safety and efficacy for CRLM measuring up to 3 cm and particularly for deep-seated CRLM or those adjacent to critical structures, reporting only low rates of major complications. Technical success rates are high, primarily using CT-guided percutaneous approaches. MWA can be repeated as a standalone treatment or combined with surgery or systemic treatments for curative intent. With a median hospitalisation of one day and evidence of improvement in global health status during follow-up in our prospective study, MWA emerges as an effective strategy for enhancing overall health outcomes and societal impacts while reducing hospitalisation durations.

6. Zusammenfassung

Die RWD unserer prospektiven Registerstudie bestätigen bereits veröffentlichte klinische Studien über die Effektivität und die Sicherheit der MWA bei CRLM der letzten Jahrzehnte. Hierzu zählt, dass die MWA eine wertvolle therapeutische Option für selektierte Patienten mit CRLM sowie für nicht operationsfähige Patienten. Die Sicherheit und Wirksamkeit der MWA ist für CRLM ≤ 3 cm Größe, insbesondere für tiefsitzende oder an kritische Strukturen angrenzende CRLM belegt, bei geringer schwerwiegender Komplikationsrate. Die MWA kann als eigenständige Behandlung wiederholt oder mit chirurgischen oder systemischen Behandlungen in kurativer Intention kombiniert werden. Die technisch erfolgreiche Durchführung der MWA ist hoch und wird hauptsächlich perkutan CT-gesteuert durchgeführt werden. In unserer prospektiven Registerstudie zeigt sich eine mediane Krankenhausverweildauer von einem Tag sowie eine Verbesserung des globalen Gesundheitszustands während der Nachbeobachtungzeit. Damit erweist sich MWA als wirksame therapeutische Strategie zur Verbesserung der Gesamtgesundheit der Patienten, zur Reduzierung der Krankenhausaufenthaltsdauer und deren gesellschaftliche Auswirkungen.

7. Bibliography

d'Abadie, P. *et al.* (2021) 'Microspheres Used in Liver Radioembolization: From Conception to Clinical Effects', *Molecules*, 26(13), p. 3966. Available at: https://doi.org/10.3390/molecules26133966.

Abdalla, E.K. *et al.* (2006) 'Improving resectability of hepatic colorectal metastases: expert consensus statement', *Annals of Surgical Oncology*, 13(10), pp. 1271–1280. Available at: https://doi.org/10.1245/s10434-006-9045-5.

Abdel-Rahman, O. (2019) 'ECOG performance score 0 versus 1: impact on efficacy and safety of first-line 5-FU-based chemotherapy among patients with metastatic colorectal cancer included in five randomized trials', *International Journal of Colorectal Disease*, 34(12), pp. 2143–2150. Available at: https://doi.org/10.1007/s00384-019-03430-y.

Abi-Jaoudeh, N. *et al.* (2012) 'Multimodality image fusion-guided procedures: technique, accuracy, and applications', *Cardiovascular and Interventional Radiology*, 35(5), pp. 986–998. Available at: https://doi.org/10.1007/s00270-012-0446-5.

Ahmed, M. *et al.* (2011a) 'Principles of and advances in percutaneous ablation', *Radiology*, 258(2), pp. 351–369. Available at: https://doi.org/10.1148/radiol.10081634.

Ahmed, M. *et al.* (2011b) 'Principles of and advances in percutaneous ablation', *Radiology*, 258(2), pp. 351–369. Available at: https://doi.org/10.1148/radiol.10081634.

Ahmed, M., Solbiati, L., Brace, C.L., Breen, D.J., Callstrom, M.R., Charboneau, J.W., Chen, M.-H., Choi, B.I., De Baère, T., Dodd, G.D., Dupuy, D.E., Gervais, D.A., Gianfelice, D., Gillams, A.R., Lee, F.T., Leen, E., Lencioni, R., Littrup, P.J., Livraghi, T., Lu, D.S., McGahan, J.P., Meloni, M.F., Nikolic, B., Pereira, P.L., Liang, P., Rhim, H., Rose, S.C., Salem, R., Sofocleous, C.T., Solomon, S.B., Soulen, M.C., Tanaka, M., Vogl, T.J., Wood, B.J. and Goldberg, S.N. (2014) 'Image-Guided Tumor Ablation: Standardization of Terminology and Reporting Criteria—A 10-Year Update', *Journal of Vascular and Interventional Radiology*, 25(11), pp. 1691-1705.e4. Available at: https://doi.org/10.1016/j.jvir.2014.08.027.

Ahmed, M., Solbiati, L., Brace, C.L., Breen, D.J., Callstrom, M.R., Charboneau, J.W., Chen, M.-H., Choi, B.I., De Baère, T., Dodd, G.D., Dupuy, D.E., Gervais, D.A., Gianfelice, D., Gillams, A.R., Lee, F.T., Leen, E., Lencioni, R., Littrup, P.J., Livraghi, T., Lu, D.S., McGahan, J.P., Meloni, M.F., Nikolic, B., Pereira, P.L., Liang, P., Rhim, H., Rose, S.C., Salem, R., Sofocleous, C.T., Solomon, S.B., Soulen, M.C., Tanaka, M., Vogl, T.J., Wood, B.J., Goldberg, S.N., *et al.* (2014) 'Image-guided Tumor Ablation: Standardization of Terminology and

Reporting Criteria—A 10-Year Update', *Radiology*, 273(1), pp. 241–260. Available at: https://doi.org/10.1148/radiol.14132958.

Akkoca, A.N. *et al.* (2014) 'TNM and Modified Dukes staging along with the demographic characteristics of patients with colorectal carcinoma', *International Journal of Clinical and Experimental Medicine*, 7(9), pp. 2828–2835.

Aragon, R.J. and Solomon, N.L. (2012) 'Techniques of hepatic resection', *Journal of Gastrointestinal Oncology*, 3(1), pp. 28–40. Available at: https://doi.org/10.3978/j.issn.2078-6891.2012.006.

de Baere, T. *et al.* (2002) 'Percutaneous radiofrequency ablation of hepatic tumors during temporary venous occlusion', *AJR. American journal of roentgenology*, 178(1), pp. 53–59. Available at: https://doi.org/10.2214/ajr.178.1.1780053.

Benedix, F. *et al.* (2012) 'Influence of anatomical subsite on the incidence of microsatellite instability, and KRAS and BRAF mutation rates in patients with colon carcinoma', *Pathology - Research and Practice*, 208(10), pp. 592–597. Available at: https://doi.org/10.1016/j.prp.2012.07.003.

Biasco, G. *et al.* (2006) 'Treatment of hepatic metastases from colorectal cancer: many doubts, some certainties', *Cancer Treatment Reviews*, 32(3), pp. 214–228. Available at: https://doi.org/10.1016/j.ctrv.2005.12.011.

Birsen, O. *et al.* (2014) 'A Critical Analysis of Postoperative Morbidity and Mortality After Laparoscopic Radiofrequency Ablation of Liver Tumors', *Annals of Surgical Oncology*, 21(6), pp. 1834–1840. Available at: https://doi.org/10.1245/s10434-014-3526-8.

Botteri, E. *et al.* (2008) 'Smoking and colorectal cancer: a meta-analysis', *JAMA*, 300(23), pp. 2765–2778. Available at: https://doi.org/10.1001/jama.2008.839.

Brace, C.L. (2010) 'Microwave tissue ablation: biophysics, technology, and applications', *Critical Reviews in Biomedical Engineering*, 38(1), pp. 65–78. Available at: https://doi.org/10.1615/critrevbiomedeng.v38.i1.60.

Buccafusca, G. *et al.* (2019) 'Early colorectal cancer: diagnosis, treatment and survivorship care', *Critical Reviews in Oncology/Hematology*, 136, pp. 20–30. Available at: https://doi.org/10.1016/j.critrevonc.2019.01.023.

Cai, S. *et al.* (2014) 'Alcohol drinking and the risk of colorectal cancer death: a meta-analysis', *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP)*, 23(6), pp. 532–539. Available at: https://doi.org/10.1097/CEJ.0000000000000076.

Calandri, M. *et al.* (2018) 'Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free

survival', *European Radiology*, 28(7), pp. 2727–2734. Available at: https://doi.org/10.1007/s00330-017-5273-2.

Cassese, G. *et al.* (2022) 'Portal vein embolization failure: Current strategies and future perspectives to improve liver hypertrophy before major oncological liver resection', *World Journal of Gastrointestinal Oncology*, 14(11), pp. 2088–2096. Available at: https://doi.org/10.4251/wjgo.v14.i11.2088.

Center, M.M. *et al.* (2009) 'Worldwide variations in colorectal cancer', *CA: a cancer journal for clinicians*, 59(6), pp. 366–378. Available at: https://doi.org/10.3322/caac.20038.

Cervantes, A. *et al.* (2023) 'Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up', *Annals of Oncology*, 34(1), pp. 10–32. Available at: https://doi.org/10.1016/j.annonc.2022.10.003.

Chan, D.S.M. *et al.* (2011) 'Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies', *PloS One*, 6(6), p. e20456. Available at: https://doi.org/10.1371/journal.pone.0020456.

Charlson, M.E. *et al.* (1987) 'A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation', *Journal of Chronic Diseases*, 40(5), pp. 373–383. Available at: https://doi.org/10.1016/0021-9681(87)90171-8.

Charnsangavej, C. *et al.* (2006) 'Selection of patients for resection of hepatic colorectal metastases: expert consensus statement', *Annals of Surgical Oncology*, 13(10), pp. 1261–1268. Available at: https://doi.org/10.1245/s10434-006-9023-y.

Choudhry, N.K. (2017) 'Randomized, Controlled Trials in Health Insurance Systems', *New England Journal of Medicine*. Edited by J.M. Drazen et al., 377(10), pp. 957–964. Available at: https://doi.org/10.1056/NEJMra1510058.

Clavien, P.A. *et al.* (2009) 'The Clavien-Dindo classification of surgical complications: five-year experience', *Annals of Surgery*, 250(2), pp. 187–196. Available at: https://doi.org/10.1097/SLA.0b013e3181b13ca2.

Dijkstra, M., Nieuwenhuizen, S., Puijk, R.S., Timmer, Florentine E. F., *et al.* (2021) 'Primary Tumor Sidedness, RAS and BRAF Mutations and MSI Status as Prognostic Factors in Patients with Colorectal Liver Metastases Treated with Surgery and Thermal Ablation: Results from the Amsterdam Colorectal Liver Met Registry (AmCORE)', *Biomedicines*, 9(8), p. 962. Available at: https://doi.org/10.3390/biomedicines9080962.

Dijkstra, M., Nieuwenhuizen, S., Puijk, R.S., Timmer, Florentine E.F., *et al.* (2021) 'Thermal Ablation Compared to Partial Hepatectomy for Recurrent Colorectal Liver Metastases: An Amsterdam Colorectal Liver Met Registry

(AmCORE) Based Study', *Cancers*, 13(11), p. 2769. Available at: https://doi.org/10.3390/cancers13112769.

Dijkstra, M. *et al.* (2023) 'Efficacy of Thermal Ablation for Small-Size (0-3 cm) versus Intermediate-Size (3-5 cm) Colorectal Liver Metastases: Results from the Amsterdam Colorectal Liver Met Registry (AmCORE)', *Cancers*, 15(17), p. 4346. Available at: https://doi.org/10.3390/cancers15174346.

Dodd, G.D. *et al.* (2005) 'Percutaneous Radiofrequency Ablation of Hepatic Tumors: Postablation Syndrome', *American Journal of Roentgenology*, 185(1), pp. 51–57. Available at: https://doi.org/10.2214/ajr.185.1.01850051.

Dodd, G.D. *et al.* (2013) 'Effect of Variation of Portal Venous Blood Flow on Radiofrequency and Microwave Ablations in a Blood-perfused Bovine Liver Model', *Radiology*, 267(1), pp. 129–136. Available at: https://doi.org/10.1148/radiol.12120486.

Donadon, M. *et al.* (2007) 'New Paradigm in the Management of Liver-Only Metastases From Colorectal Cancer', 1(1), p. 8.

Dykes, T.M., Bhargavan-Chatfield, M. and Dyer, R.B. (2015) 'Intravenous contrast extravasation during CT: a national data registry and practice quality improvement initiative', *Journal of the American College of Radiology: JACR*, 12(2), pp. 183–191. Available at: https://doi.org/10.1016/j.jacr.2014.07.021.

Elfrink, A.K.E. *et al.* (2021) 'Hospital variation in combined liver resection and thermal ablation for colorectal liver metastases and impact on short-term postoperative outcomes: a nationwide population-based study', *HPB*, 23(6), pp. 827–839. Available at: https://doi.org/10.1016/j.hpb.2020.10.003.

Ferlay, J. *et al.* (2015) 'Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012', *International Journal of Cancer*, 136(5), pp. E359-386. Available at: https://doi.org/10.1002/ijc.29210.

Filippiadis, D.K. *et al.* (2017) 'Cirse Quality Assurance Document and Standards for Classification of Complications: The Cirse Classification System', *CardioVascular and Interventional Radiology*, 40(8), pp. 1141–1146. Available at: https://doi.org/10.1007/s00270-017-1703-4.

Fong, Y. *et al.* (1999) 'Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases', *Annals of Surgery*, 230(3), pp. 309–318; discussion 318-321. Available at: https://doi.org/10.1097/00000658-199909000-00004.

Ford, I. and Norrie, J. (2016) 'Pragmatic Trials', *New England Journal of Medicine*. Edited by J.M. Drazen et al., 375(5), pp. 454–463. Available at: https://doi.org/10.1056/NEJMra1510059.

Freites-Martinez, A. *et al.* (2021) 'Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse

Events of Anticancer Therapies', *Actas Dermo-Sifiliograficas*, 112(1), pp. 90–92. Available at: https://doi.org/10.1016/j.ad.2019.05.009.

Gage, A.A. and Baust, J. (1998) 'Mechanisms of tissue injury in cryosurgery', *Cryobiology*, 37(3), pp. 171–186. Available at: https://doi.org/10.1006/cryo.1998.2115.

Geschwind, J.-F.H. *et al.* (2002) 'Influence of a New Prophylactic Antibiotic Therapy on the Incidence of Liver Abscesses after Chemoembolization Treatment of Liver Tumors', *Journal of Vascular and Interventional Radiology*, 13(11), pp. 1163–1166. Available at: https://doi.org/10.1016/S1051-0443(07)61959-9.

Gillams, A. *et al.* (2015) 'Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontières meeting 2013', *European Radiology*, 25(12), pp. 3438–3454. Available at: https://doi.org/10.1007/s00330-015-3779-z.

Gliklich, R.E., Dreyer, N.A. and Leavy, M.B. (eds) (2014) *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd edn. Rockville (MD): Agency for Healthcare Research and Quality (US) (AHRQ Methods for Effective Health Care). Available at: http://www.ncbi.nlm.nih.gov/books/NBK208616/ (Accessed: 4 June 2024).

Goldberg, S.N. *et al.* (1998) 'Radio-frequency tissue ablation: effect of pharmacologic modulation of blood flow on coagulation diameter.', *Radiology*, 209(3), pp. 761–767. Available at: https://doi.org/10.1148/radiology.209.3.9844671.

Goldberg, S.N. *et al.* (2003) 'Image-guided tumor ablation: proposal for standardization of terms and reporting criteria', *Radiology*, 228(2), pp. 335–345. Available at: https://doi.org/10.1148/radiol.2282021787.

Gravante, G. *et al.* (2008) 'Hepatic microwave ablation: a review of the histological changes following thermal damage', *Liver International*, 28(7), pp. 911–921. Available at: https://doi.org/10.1111/j.1478-3231.2008.01810.x.

Groeschl, R.T. *et al.* (2014) 'Microwave Ablation for Hepatic Malignancies: A Multiinstitutional Analysis', *Annals of Surgery*, 259(6), pp. 1195–1200. Available at: https://doi.org/10.1097/SLA.0000000000000234.

Guiu, B. *et al.* (2016) 'Simultaneous trans-hepatic portal and hepatic vein embolization before major hepatectomy: the liver venous deprivation technique', *European Radiology*, 26(12), pp. 4259–4267. Available at: https://doi.org/10.1007/s00330-016-4291-9.

de Haas, R.J. *et al.* (2011a) 'Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic

resection', *Annals of Surgery*, 253(6), pp. 1069–1079. Available at: https://doi.org/10.1097/SLA.0b013e318217e898.

de Haas, R.J. *et al.* (2011b) 'Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic resection', *Annals of Surgery*, 253(6), pp. 1069–1079. Available at: https://doi.org/10.1097/SLA.0b013e318217e898.

Hao, M.-Z. *et al.* (2022) 'Efficacy and safety of computed tomography-guided microwave ablation with fine needle-assisted puncture positioning technique for hepatocellular carcinoma', *World Journal of Gastrointestinal Oncology*, 14(9), pp. 1727–1738. Available at: https://doi.org/10.4251/wjgo.v14.i9.1727.

Helmberger, T. *et al.* (2022) 'Safety, Feasibility and Technical Considerations from a Prospective, Observational Study—CIREL: Irinotecan-TACE for CRLM in 152 Patients', *Journal of Clinical Medicine*, 11(20), p. 6178. Available at: https://doi.org/10.3390/jcm11206178.

Henrikson, N.B. *et al.* (2015) 'Family history and the natural history of colorectal cancer: systematic review', *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 17(9), pp. 702–712. Available at: https://doi.org/10.1038/gim.2014.188.

Hoffmann, R.T. *et al.* (2011) 'Arterial therapies of non-colorectal cancer metastases to the liver (from chemoembolization to radioembolization)', *Abdominal Imaging*, 36(6), pp. 671–676. Available at: https://doi.org/10.1007/s00261-011-9753-6.

Hong, S.J. *et al.* (2016) 'Characteristics and Quality of Radiologic Randomized Controlled Trials: A Bibliometric Analysis Between 1995 and 2014', *American Journal of Roentgenology*, 206(5), pp. 917–923. Available at: https://doi.org/10.2214/AJR.15.15640.

Ioannidis, J.P. *et al.* (2001) 'Comparison of evidence of treatment effects in randomized and nonrandomized studies', *JAMA*, 286(7), pp. 821–830. Available at: https://doi.org/10.1001/jama.286.7.821.

Ioannidis, J.P.A. (2001) 'Any casualties in the clash of randomised and observational evidence?', *BMJ*, 322(7291), pp. 879–880. Available at: https://doi.org/10.1136/bmj.322.7291.879.

Jarnagin, W.R. *et al.* (2002) 'Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade', *Annals of Surgery*, 236(4), pp. 397–406; discussion 406-407. Available at: https://doi.org/10.1097/01.SLA.0000029003.66466.B3.

Jiao, S. *et al.* (2014) 'Estimating the heritability of colorectal cancer', *Human Molecular Genetics*, 23(14), pp. 3898–3905. Available at: https://doi.org/10.1093/hmg/ddu087.

Johnson, C.M. *et al.* (2013) ‘Meta-analyses of colorectal cancer risk factors’, *Cancer Causes & Control*, 24(6), pp. 1207–1222. Available at: https://doi.org/10.1007/s10552-013-0201-5.

Kalantzis, I. *et al.* (2020) ‘Clinicopathological differences and correlations between right and left colon cancer’, *World Journal of Clinical Cases*, 8(8), pp. 1424–1443. Available at: https://doi.org/10.12998/wjcc.v8.i8.1424.

Kemeny, M.M. (2006) ‘Expressing the Surgery First Position on Treatment of Synchronous Colorectal Metastases in the Asymptomatic Patient’, *Annals of Surgical Oncology*, 13(2), pp. 140–141. Available at: https://doi.org/10.1245/ASO.2006.07.028.

Khoo, E. *et al.* (2016) ‘Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases’, *HPB: the official journal of the International Hepato Pancreato Biliary Association*, 18(6), pp. 485–493. Available at: https://doi.org/10.1016/j.hpb.2016.03.001.

Kim, Y.-S. *et al.* (2010) ‘The minimal ablative margin of radiofrequency ablation of hepatocellular carcinoma (> 2 and < 5 cm) needed to prevent local tumor progression: 3D quantitative assessment using CT image fusion’, *AJR. American journal of roentgenology*, 195(3), pp. 758–765. Available at: https://doi.org/10.2214/AJR.09.2954.

Knott, E.A. *et al.* (2021) ‘Microwave ablation for colorectal cancer metastasis to the liver: a single-center retrospective analysis’, *Journal of Gastrointestinal Oncology*, 12(4), pp. 1454–1469. Available at: https://doi.org/10.21037/jgo-21-159.

Kokkotou, E. *et al.* (2024) ‘Real-World Data and Evidence in Lung Cancer: A Review of Recent Developments’, *Cancers*, 16(7), p. 1414. Available at: https://doi.org/10.3390/cancers16071414.

Krämer, H.U. *et al.* (2012) ‘Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences’, *European Journal of Cancer (Oxford, England: 1990)*, 48(9), pp. 1269–1282. Available at: https://doi.org/10.1016/j.ejca.2011.07.010.

Kyrgiou, M. *et al.* (2017) ‘Adiposity and cancer at major anatomical sites: umbrella review of the literature’, *BMJ (Clinical research ed.)*, 356, p. j477. Available at: https://doi.org/10.1136/bmj.j477.

Laimer, G., Schullian, P. and Bale, R. (2021) ‘Stereotactic Thermal Ablation of Liver Tumors: 3D Planning, Multiple Needle Approach, and Intraprocedural Image Fusion Are the Key to Success—A Narrative Review’, *Biology*, 10(7), p. 644. Available at: https://doi.org/10.3390/biology10070644.

Lalmahomed, Z.S. *et al.* (2011) ‘Anatomical versus nonanatomical resection of colorectal liver metastases: is there a difference in surgical and oncological

outcome?', *World Journal of Surgery*, 35(3), pp. 656–661. Available at: https://doi.org/10.1007/s00268-010-0890-9.

Langley, R.R. and Fidler, I.J. (2011) 'The seed and soil hypothesis revisited--the role of tumor-stroma interactions in metastasis to different organs', *International Journal of Cancer*, 128(11), pp. 2527–2535. Available at: https://doi.org/10.1002/ijc.26031.

Leonard, G.D., Brenner, B. and Kemeny, N.E. (2005) 'Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma', *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 23(9), pp. 2038–2048. Available at: https://doi.org/10.1200/JCO.2005.00.349.

Lewandowski, R. and Salem, R. (2006) 'Yttrium-90 Radioembolization of Hepatocellular Carcinoma and Metastatic Disease to the Liver', *Seminars in Interventional Radiology*, 23(1), pp. 064–072. Available at: https://doi.org/10.1055/s-2006-939842.

Lewandowski, R.J. *et al.* (2011) 'Transcatheter Intraarterial Therapies: Rationale and Overview', *Radiology*, 259(3), pp. 641–657. Available at: https://doi.org/10.1148/radiol.11081489.

Li Destri, G. *et al.* (2008) 'Metachronous liver metastases and resectability: Fong's score and laparoscopic evaluation', *HPB: the official journal of the International Hepato Pancreato Biliary Association*, 10(1), pp. 13–17. Available at: https://doi.org/10.1080/13651820701851384.

Liang, P. *et al.* (2009) 'Malignant Liver Tumors: Treatment with Percutaneous Microwave Ablation—Complications among Cohort of 1136 Patients', *Radiology*, 251(3), pp. 933–940. Available at: https://doi.org/10.1148/radiol.2513081740.

Lin, Y.-M. *et al.* (2021) 'Image-Guided Ablation for Colorectal Liver Metastasis: Principles, Current Evidence, and the Path Forward', *Cancers*, 13(16), p. 3926. Available at: https://doi.org/10.3390/cancers13163926.

Liu, W. *et al.* (2019) 'The primary tumor location impacts survival outcome of colorectal liver metastases after hepatic resection: A systematic review and meta-analysis', *European Journal of Surgical Oncology*, 45(8), pp. 1349–1356. Available at: https://doi.org/10.1016/j.ejso.2019.04.017.

Livraghi, T. *et al.* (2012) 'Complications of microwave ablation for liver tumors: results of a multicenter study', *Cardiovascular and Interventional Radiology*, 35(4), pp. 868–874. Available at: https://doi.org/10.1007/s00270-011-0241-8.

Lu, D.S.K. *et al.* (2002) 'Effect of Vessel Size on Creation of Hepatic Radiofrequency Lesions in Pigs: Assessment of the "Heat Sink" Effect',

American Journal of Roentgenology, 178(1), pp. 47–51. Available at: https://doi.org/10.2214/ajr.178.1.1780047.

Lubner, M.G. *et al.* (2010) 'Microwave Tumor Ablation: Mechanism of Action, Clinical Results, and Devices', *Journal of Vascular and Interventional Radiology*, 21(8), pp. S192–S203. Available at: https://doi.org/10.1016/j.jvir.2010.04.007.

Maher, B. *et al.* (2017) 'The management of colorectal liver metastases', *Clinical Radiology*, 72(8), pp. 617–625. Available at: https://doi.org/10.1016/j.crad.2017.05.016.

Mahnken, A. *et al.* (2009) 'CT-gesteuerte Radiofrequenzablation von Lebermetastasen kolorektaler Tumoren', *DMW - Deutsche Medizinische Wochenschrift*, 134(19), pp. 976–980. Available at: https://doi.org/10.1055/s-0029-1222553.

Mann, C.D. *et al.* (2010) 'The safety and efficacy of ablative techniques adjacent to the hepatic vasculature and biliary system', *ANZ Journal of Surgery*, 80(1–2), pp. 41–49. Available at: https://doi.org/10.1111/j.1445-2197.2009.05174.x.

Massmann, A. *et al.* (2015) 'Transarterial chemoembolization (TACE) for colorectal liver metastases—current status and critical review', *Langenbeck's Archives of Surgery*, 400(6), pp. 641–659. Available at: https://doi.org/10.1007/s00423-015-1308-9.

Mauri, G. *et al.* (2015) 'Real-Time US-CT/MRI Image Fusion for Guidance of Thermal Ablation of Liver Tumors Undetectable with US: Results in 295 Cases', *CardioVascular and Interventional Radiology*, 38(1), pp. 143–151. Available at: https://doi.org/10.1007/s00270-014-0897-y.

Medema, J.P. (2013) 'Cancer stem cells: the challenges ahead', *Nature Cell Biology*, 15(4), pp. 338–344. Available at: https://doi.org/10.1038/ncb2717.

Meloni, M.F. *et al.* (2017) 'Microwave ablation in primary and secondary liver tumours: technical and clinical approaches', *International Journal of Hyperthermia*, 33(1), pp. 15–24. Available at: https://doi.org/10.1080/02656736.2016.1209694.

Mishra-Kalyani, P.S. *et al.* (2022) 'External control arms in oncology: current use and future directions', *Annals of Oncology*, 33(4), pp. 376–383. Available at: https://doi.org/10.1016/j.annonc.2021.12.015.

Mitchell, D., Puckett, Y. and Nguyen, Q.N. (2019) 'Literature Review of Current Management of Colorectal Liver Metastasis', *Cureus*, 11(1), p. e3940. Available at: https://doi.org/10.7759/cureus.3940.

Mulier, S. *et al.* (2002) ‘Complications of radiofrequency coagulation of liver tumours’, *British Journal of Surgery*, 89(10), pp. 1206–1222. Available at: https://doi.org/10.1046/j.1365-2168.2002.02168.x.

Nassabein, R. *et al.* (2021) ‘Outcomes of Older Patients with Resectable Colorectal Liver Metastases Cancer (CRLM): Single Center Experience’, *Current Oncology (Toronto, Ont.)*, 28(3), pp. 1899–1908. Available at: https://doi.org/10.3390/curroncol28030176.

Nassar, D. and Blanpain, C. (2016) ‘Cancer Stem Cells: Basic Concepts and Therapeutic Implications’, *Annual Review of Pathology*, 11, pp. 47–76. Available at: https://doi.org/10.1146/annurev-pathol-012615-044438.

Nasseri, Y. and Langenfeld, S.J. (2017) ‘Imaging for Colorectal Cancer’, *Surgical Clinics of North America*, 97(3), pp. 503–513. Available at: https://doi.org/10.1016/j.suc.2017.01.002.

Neumann, E. *et al.* (1982) ‘Gene transfer into mouse lyoma cells by electroporation in high electric fields’, *The EMBO journal*, 1(7), pp. 841–845. Available at: https://doi.org/10.1002/j.1460-2075.1982.tb01257.x.

Niekel, M.C., Bipat, S. and Stoker, J. (2010) ‘Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment’, *Radiology*, 257(3), pp. 674–684. Available at: https://doi.org/10.1148/radiol.10100729.

Nieuwenhuizen, S. *et al.* (2020) ‘Resectability and Ablatability Criteria for the Treatment of Liver Only Colorectal Metastases: Multidisciplinary Consensus Document from the COLLISION Trial Group’, *Cancers*, 12(7), p. 1779. Available at: https://doi.org/10.3390/cancers12071779.

Odisio, B.C. *et al.* (2017) ‘Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status’, *The British Journal of Surgery*, 104(6), pp. 760–768. Available at: https://doi.org/10.1002/bjs.10490.

Ozen, M. and Raissi, D. (2022) ‘Current perspectives on microwave ablation of liver lesions in difficult locations’, *Journal of Clinical Imaging Science*, 12, p. 61. Available at: https://doi.org/10.25259/JCIS_126_2022.

Pereira, P.L. *et al.* (2021) ‘The CIREL Cohort: A Prospective Controlled Registry Studying the Real-Life Use of Irinotecan-Loaded Chemoembolisation in Colorectal Cancer Liver Metastases: Interim Analysis’, *CardioVascular and Interventional Radiology*, 44(1), pp. 50–62. Available at: https://doi.org/10.1007/s00270-020-02646-8.

Philippe L. Pereira, Chrstof-Matthias Sommer (2015) *Modern Practice of Transarterial Tumour Therapy of the Liver*. 1st edn. Bremen: UNI-MED SCIENCE.

Philips, P. *et al.* (2016) 'Single-stage resection and microwave ablation for bilobar colorectal liver metastases', *The British Journal of Surgery*, 103(8), pp. 1048–1054. Available at: https://doi.org/10.1002/bjs.10159.

Poon, R.T. *et al.* (2004) 'Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database', *Annals of Surgery*, 240(4), pp. 698–708; discussion 708-710. Available at: https://doi.org/10.1097/01.sla.0000141195.66155.0c.

Popat, S. *et al.* (2022) 'Addressing challenges with real-world synthetic control arms to demonstrate the comparative effectiveness of Pralsetinib in non-small cell lung cancer', *Nature Communications*, 13(1), p. 3500. Available at: https://doi.org/10.1038/s41467-022-30908-1.

Price, D. *et al.* (2011) 'Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy', *New England Journal of Medicine*, 364(18), pp. 1695–1707. Available at: https://doi.org/10.1056/NEJMoa1010846.

Puijk, R.S. *et al.* (2022) 'Improved Outcomes of Thermal Ablation for Colorectal Liver Metastases: A 10-Year Analysis from the Prospective Amsterdam CORE Registry (AmCORE)', *CardioVascular and Interventional Radiology*, 45(8), pp. 1074–1089. Available at: https://doi.org/10.1007/s00270-022-03152-9.

Resnic, F.S. *et al.* (2017) 'Registry-Based Prospective, Active Surveillance of Medical-Device Safety', *New England Journal of Medicine*, 376(6), pp. 526–535. Available at: https://doi.org/10.1056/NEJMoa1516333.

Rhaiem, R. *et al.* (2020) 'Microwave Thermoablation of Colorectal Liver Metastases Close to Large Hepatic Vessels Under Pringle Maneuver Minimizes the "Heat Sink Effect"', *World Journal of Surgery*, 44(5), pp. 1595–1603. Available at: https://doi.org/10.1007/s00268-020-05379-4.

Riihimäki, M. *et al.* (2016a) 'Patterns of metastasis in colon and rectal cancer', *Scientific Reports*, 6(1), p. 29765. Available at: https://doi.org/10.1038/srep29765.

Riihimäki, M. *et al.* (2016b) 'Patterns of metastasis in colon and rectal cancer', *Scientific Reports*, 6(1), p. 29765. Available at: https://doi.org/10.1038/srep29765.

Ringe, K.I. *et al.* (2015) 'Experimental Evaluation of the Heat Sink Effect in Hepatic Microwave Ablation', *PloS One*, 10(7), p. e0134301. Available at: https://doi.org/10.1371/journal.pone.0134301.

Rubinsky, B. *et al.* (1990) 'The process of freezing and the mechanism of damage during hepatic cryosurgery', *Cryobiology*, 27(1), pp. 85–97. Available at: https://doi.org/10.1016/0011-2240(90)90055-9.

Sacks, D. *et al.* (2003) 'Society of Interventional Radiology Clinical Practice Guidelines', *Journal of Vascular and Interventional Radiology*, 14(9), pp. S199–S202. Available at: https://doi.org/10.1097/01.RVI.0000094584.83406.3e.

Schoen, R.E. *et al.* (2015) 'Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer', *Gastroenterology*, 149(6), pp. 1438-1445.e1. Available at: https://doi.org/10.1053/j.gastro.2015.07.055.

Schwartz, D. and Lellouch, J. (1967) 'Explanatory and pragmatic attitudes in therapeutical trials', *Journal of Chronic Diseases*, 20(8), pp. 637–648. Available at: https://doi.org/10.1016/0021-9681(67)90041-0.

Shady, W. *et al.* (2017) 'Kras mutation is a marker of worse oncologic outcomes after percutaneous radiofrequency ablation of colorectal liver metastases', *Oncotarget*, 8(39), pp. 66117–66127. Available at: https://doi.org/10.18632/oncotarget.19806.

Shady, W. *et al.* (2018) 'Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control', *Journal of Vascular and Interventional Radiology*, 29(2), pp. 268-275.e1. Available at: https://doi.org/10.1016/j.jvir.2017.08.021.

Simon, C.J., Dupuy, D.E. and Mayo-Smith, W.W. (2005) 'Microwave Ablation: Principles and Applications', *RadioGraphics*, 25(suppl_1), pp. S69–S83. Available at: https://doi.org/10.1148/rg.25si055501.

Sommer, C.M. *et al.* (2013) 'Bipolar versus multipolar radiofrequency (RF) ablation for the treatment of renal cell carcinoma: differences in technical and clinical parameters', *International Journal of Hyperthermia: The Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, 29(1), pp. 21–29. Available at: https://doi.org/10.3109/02656736.2012.750015.

Song, P. *et al.* (2017) 'The clinical utility and outcomes of microwave ablation for colorectal cancer liver metastases', *Oncotarget*, 8(31), pp. 51792–51799. Available at: https://doi.org/10.18632/oncotarget.15244.

Stangl, R. *et al.* (1994) 'Factors influencing the natural history of colorectal liver metastases', *The Lancet*, 343(8910), pp. 1405–1410. Available at: https://doi.org/10.1016/S0140-6736(94)92529-1.

Syngal, S. *et al.* (2015) 'ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes', *The American*

Journal of Gastroenterology, 110(2), pp. 223–262; quiz 263. Available at: https://doi.org/10.1038/ajg.2014.435.

Takahashi, H., Kahramangil, B. and Berber, E. (2018) 'Local recurrence after microwave thermosphere ablation of malignant liver tumors: results of a surgical series', *Surgery*, 163(4), pp. 709–713. Available at: https://doi.org/10.1016/j.surg.2017.10.026.

Takamura, M. *et al.* (2001) 'Microwave Coagulation Therapy with Interruption of Hepatic Blood Inor Outflow: An Experimental Study', *Journal of Vascular and Interventional Radiology*, 12(5), pp. 619–622. Available at: https://doi.org/10.1016/S1051-0443(07)61487-0.

Tanaka, K. *et al.* (2006) 'Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver', *Surgery*, 139(2), pp. 263–273. Available at: https://doi.org/10.1016/j.surg.2005.07.036.

Tinguely, P. *et al.* (2023) 'A prospective multicentre trial on survival after Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases (MAVERRIC)', *European Journal of Cancer*, 187, pp. 65–76. Available at: https://doi.org/10.1016/j.ejca.2023.03.038.

Torzilli, G. *et al.* (2017) 'Surgery of Colorectal Liver Metastases: Pushing the Limits', *Liver Cancer*, 6(1), pp. 80–89. Available at: https://doi.org/10.1159/000449495.

Uberoi, R. *et al.* (2012) 'British Society of Interventional Radiology: Biliary Drainage and Stenting Registry (BDSR)', *Cardiovascular and Interventional Radiology*, 35(1), pp. 127–138. Available at: https://doi.org/10.1007/s00270-011-0103-4.

U.S. Department of Health and Human Services (2017) 'Common Terminology Criteria for Adverse Events (CTCAE)'.

Van Duijnhoven, F.H. *et al.* (2006) 'Factors Influencing the Local Failure Rate of Radiofrequency Ablation of Colorectal Liver Metastases', *Annals of Surgical Oncology*, 13(5), pp. 651–658. Available at: https://doi.org/10.1245/ASO.2006.08.014.

Viadana, E., Bross, I.D. and Pickren, J.W. (1978) 'The metastatic spread of cancers of the digestive system in man', *Oncology*, 35(3), pp. 114–126. Available at: https://doi.org/10.1159/000225269.

Vo Chieu, V.D. *et al.* (2018) 'CT-Guided Microwave Ablation of Liver Tumors in Anatomically Challenging Locations', *CardioVascular and Interventional Radiology*, 41(10), pp. 1520–1529. Available at: https://doi.org/10.1007/s00270-018-2007-z.

Vogl, T. *et al.* (2017) 'Microwave Ablation (MWA): Basics, Technique and Results in Primary and Metastatic Liver Neoplasms – Review Article', *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren*, 189(11), pp. 1055–1066. Available at: https://doi.org/10.1055/s-0043-117410.

Wang, M. and Kohi, M. (2018) 'Paving the Path to Value: The Role of Registry Studies in Interventional Radiology', *Journal of Clinical Interventional Radiology ISVIR*, 02(02), pp. 128–132. Available at: https://doi.org/10.1055/s-0038-1667207.

Wang, X. *et al.* (2013) 'Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases', *Cardiovascular and Interventional Radiology*, 36(1), pp. 166–175. Available at: https://doi.org/10.1007/s00270-012-0377-1.

Weiss, L. *et al.* (1986) 'Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies', *The Journal of Pathology*, 150(3), pp. 195–203. Available at: https://doi.org/10.1002/path.1711500308.

Wong, S.L. *et al.* (2010) 'American Society of Clinical Oncology 2009 Clinical Evidence Review on Radiofrequency Ablation of Hepatic Metastases From Colorectal Cancer', *Journal of Clinical Oncology*, 28(3), pp. 493–508. Available at: https://doi.org/10.1200/JCO.2009.23.4450.

Yu, J. and Liang, P. (2017) 'Status and advancement of microwave ablation in China', *International Journal of Hyperthermia*, 33(3), pp. 278–287. Available at: https://doi.org/10.1080/02656736.2016.1243261.

Yu, N.C. *et al.* (2008) 'Microwave Liver Ablation: Influence of Hepatic Vein Size on Heat-sink Effect in a Porcine Model', *Journal of Vascular and Interventional Radiology*, 19(7), pp. 1087–1092. Available at: https://doi.org/10.1016/j.jvir.2008.03.023.

Zorzi, D. *et al.* (2006) 'Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases', *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract*, 10(1), pp. 86–94. Available at: https://doi.org/10.1016/j.gassur.2005.07.022.

Zorzi, D. *et al.* (2007) 'Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases', *The British Journal of Surgery*, 94(3), pp. 274–286. Available at: https://doi.org/10.1002/bjs.5719.

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Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

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