Chapter

Magnetic Resonance-Guided Focused Ultrasound in the Treatment of Colorectal Cancer Liver Metastases

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Abstract

Liver metastases often result secondary to colorectal cancer and curative prognosis is poor. Magnetic resonance high intensity focused ultrasound is a bur-geoning technique with the potential to provide a new image-guidance modality for focused ultrasound ablation of both primary and secondary liver tumors. This is particularly important for colorectal liver metastases cases ineligible for surgical resection, as chemotherapy can often be ineffective at bridging the patient for surgery, and liver transplant has generally been inadequate. At least one system for focused ultrasound ablation of primary and secondary tumors has previously been approved in the European Union, under ultrasound guidance. Magnetic resonance guidance offers many benefits, such as: integration with pre-existing imaging systems, real-time temperature mapping, and ability to assess treatment with MRI during the procedure. This chapter reviews the main aspects in treatment of this disease using this new therapy, including: focused ultrasound physics, magnetic resonance physics, magnetic resonance sequences and protocols in liver imaging, protocols and sequences in magnetic resonance thermometry, standard treatment options and limitations, relevant ongoing clinical trials, previous pilot studies, and outlooks for potential translation of this image-guidance modality as a novel ablative therapy for colorectal liver metastases.

Keywords: interventional radiology, focused ultrasound, liver cancer, thermal ablation, colorectal liver metastases

1. Introduction

Open surgery generally offers the best long-term survival rates for colorectal liver metastases (CRLM); with minimally invasive techniques becoming more common [1]. Magnetic resonance guided high intensity focused ultrasound (MRgHIFU) is noninvasive and non-ionizing, allowing for reduced treatment morbidity. At least one system for ultrasound guided focused ultrasound (USgFUS) ablation has been approved within the European Union for primary and secondary hepatic tumors [2].

Although, liver metastases are more common than primary liver tumors, most focused ultrasound studies report outcomes for primary hepatocellular carcinoma (HCC). The use of MRgHIFU for both primary and secondary hepatobiliary tumors is still awaiting certification and has not yet been reported in randomized controlled trials for CRLM or HCC [3]. Discussed here are the focused ultrasound (FUS) physics, the principles of MRI for liver metastases, analysis of the standard treatment approaches for CRLM, and previous studies involving ablation of liver tumors with USgFUS and MRgHIFU.

In 2019, cancer was reported to be the second leading cause of death, globally; amounting to approximately 1 in 6 deaths, worldwide [4]. The primary cause was due to exogenous factors resulting in genetic mutations and amounts to about 90% of reported cases [5]. P53 mutations in tumor suppressor genes are estimated in about 50% of cancers and RAS gene mutations of proto-oncogenes are estimated in about 30% of cancers. Tobacco use is thought to account for the majority of all cancer deaths. This is followed by high body mass index, alcohol use, and malnutrition [5].

HCC is the most common primary liver tumor type. There were approximately 906,000 new primary liver cancer cases in 2020, of which 75–85% were HCC, arriving at approximately 679,500–770,100 new HCC cases [6]. The most prevalent underlying conditions for HCC are Hepatitis-B virus, Hepatitis-C virus, and liver cirrhosis [7, 8]. Primary liver tumor treatment depends on history and staging. If HCC results from decompensated liver cirrhosis, surgical resection is not recommended. These patients do have the option of total liver transplant with 5-year survival rates of about 60–70%. Curative treatment options for late-stage diagnosis or recurrence is rare [8–10]. For HCC, the 10-year survival rate after surgical resection is approximately 25% [11]. However, liver transplant often offers much better outcomes than surgery for HCC. With liver transplant for patients meeting the Milan criteria, 5-year survival rates are near 70%, with less than 10% recurrence rates [11–13]. Liver transplant for HCC constitutes about 25% of liver transplants in the USA and about 40% of liver transplants in Europe [14].

CRLM is the most common form of secondary liver tumor [15]. CRLM occurs in about one-third to one-half of adult CRC cases and the liver metastases is the cause of death in about two-thirds of these patients [16]. In 2020, there were approximately 1.9 million new cases of CRC, of which it might be expected that 633,333–950,000 developed liver metastases [6]. Diagnostic radiologists have listed secondary liver tumor sites at 18–40 times more frequent than primary liver tumors, as the condition often presents with multiple metastases [17]. Historically, CRLM was deemed incurable with untreated 5-year survival rates of less than 2% [18]. Survival rates of patients with distant secondary metastatic tumors can be improved with surgical treatment and systemic chemotherapy [8, 19, 20]. Pediatric liver metastasis is more often secondary to Wilms' tumors or neuroblastomas rather than CRC [21, 22]. About 15% of adult patients exhibit liver metastasis at initial CRC diagnosis [23] and about 70% develop CRLM [2]. Approximately 60% of CRC deaths result from liver metastases [23, 24]. The standard treatment for CRLM is liver resection and is largely considered the best option for long-term curative potential [1, 8, 25, 26], with about a 40% survival rate after 5 years [2, 8, 23, 27], about a 24% survival rate after 10 years [2, 28], about a 20% cure rate [28], and a median survival rate of approximately 30 months [29]. However, for both HCC and CRLM, surgical eligibility is only 20–25% [2]. Liver transplant for CRLM has given good results in recent clinical trials when using tighter inclusion criteria and molecular profiling [30–32], although has historically given dismal survival rates, with high incidence of recurrence, survival rates only marginally better than systemic chemotherapy, and is not a primary option in

standard treatment algorithms [1, 33]. Hence, CRLM has an additional treatment difficulty, compared to HCC, because liver transplant does not generally provide long term survival.

2. Focused ultrasound principles

FUS surgery was first reported in 1942 after being applied to cat and dog brain tissue [34, 35] and more elaborate neurological studies later followed [36, 37]. MRgHIFU integrates a FUS transducer into a MRI system with near real-time imaging feedback; capable of temporal resolution less than 1.0 seconds, in-plane resolution less than 1.0 mm, and temperature resolution less than 1.0°C [34]. Thermal tissue ablation results from rapid temperature change of greater than 55°C during heating or −20 to −50°C during cooling [38]. Adequate ablation for coagulative necrosis requires about 10 seconds, with intermittent cooling periods to avoid skin burning [34]. More recent developments enable various feedback methods to regulate temperature, optimize speed, and automate the scanning procedure [39].

FUS works via constructive wave interference. The waves are generated by powering piezoelectric elements with an alternating current [40]. Most modern transducers are phase-array types, composed of hundreds of elements that can be individually controlled, each emitting a low amplitude ultrasonic wave at the focus [40]. Each wave is low enough in amplitude to pass through the tissue without causing significant heating, interfering constructively at the focus. The phase lag of each transducer element is adjusted so the waves are in-phase at the focal region, capable of performing beam steering and refocusing phase aberrations from bone or tissue inhomogeneities. When the waves form a large amplitude oscillation, the heating increases substantially and allows ablation and coagulative necrosis. The wave amplitude and frequency can be controlled by the operator as well as other factors like position, applied power, and pulse modulation. Lower frequencies are better for deep sites like transcranial applications, while high frequencies are used for surface sites [41].

Tissue has an inherent property to absorb ultrasonic energy. The acoustic absorption coefficient measures a tissue's ability to absorb ultrasound. In tissue at 1 MHz, the beam attenuates to about 50% at a depth of about 7 cm [38]. Beam reflection is significant at interfaces with large differences in acoustic absorption coefficient, causing high amounts of reflection at tissue-gas interfaces and tissue-bone interfaces [38]. At large FUS powers, strong rarefactional pressures exist. If this is coupled with lower frequency ultrasound waves, the conditions are favorable to induce tissue nucleation [34, 42]. This results in cavitational heating that can cause detrimental tissue damage or be utilized in techniques like lithotripsy [43, 44] and histotripsy [45, 46]. Low temperature therapies expose cells to about 43–45°C for long time periods. High temperature thermal therapy uses temperature between 50°C and 80°C for short time periods to ablate tissue, cause coagulation, and induce necrosis [47]. The tissue damage is estimated by the equivalent number of thermal doses at 43°C, with necrosis induced after about 240 min at 43°C [48, 49].

3. MRI principles

MRI is based on the concept of nuclear magnetic resonance. Atomic nuclei with an odd number of protons or neutrons exhibit a net spin entailing a charge circulation that forms an individual magnetic field surrounding the atom, giving the protons a

magnetic dipole [50–55]. As the hydrogen atoms exhibit ±½ spin, and the nuclear spins exist in two states that are randomly oriented, in absence of a net magnetic field, there is no overall net magnetization. When placed in an external magnetic field, the spins orient parallel and anti-parallel to the direction of the B_0 magnetic field, with a slight propensity for the spins to align in the parallel direction, causing the tissue to express a net equilibrium magnetization [50, 53]. The magnetic moment of the atom rotates like a spinning top, predominately in the direction of the applied magnetic field. This magnetic moment rotates at an angular frequency unique to individual atoms, termed the Larmor frequency.

When a perpendicular radiofrequency field (B_1) is applied at the hydrogen Larmor resonance frequency, only the protons absorb energy, and are tipped from the direction of the main magnetic field, with the flip angle denoting the degree that the spins are displaced from the equilibrium B_0 direction [55]. This excites the protons to precess in a rotational motion around the B_0 field vector. The excited proton magnetization vector then relaxes in the direction of the main B_0 magnetic field, generating a longitudinal and transverse time-varying magnetization signal that is detected by the MRI receiver coils.

The rate at which this magnetization vector relaxes towards the main magnetic field direction is measured in terms of spin-lattice relaxation (T_1) in the direction of the B_0 magnetic field, and the spin-spin relaxation rate (T_2) trans-verse to the B_0 magnetic field direction [50, 53]. The T_1 and T_2 decay rates result from random static magnetic field variations. However, the relaxation rates are also influenced by time varying factors, such as magnetic field inhomogeneities, that combine with tissue static magnetic field to affect the relaxation rate.

The net magnetism applied to each proton results from both the field generated from the MRI system, in addition to the fields generated by the surrounding protons and bulk susceptibility [55, 56]. A chemical shift in the precession frequency results from the magnetic fields generated from these surrounding protons. This can allow identification of specific molecules present in the tissue, that introduce a distinctive chemical shift in the MR signal [55]. The degree of this shift also has a temperature dependence. Using the principle of proton resonance frequency shift (PRFS) thermometry, the individual temperature of each voxel can be quantified from the resulting temperature-dependent phase change due to this chemical shift [56].

4. MRI liver imaging

Radiological imaging is used in a variety of manners in treating CRLM: including, to diagnose a condition, stage the disease, to locate extra-hepatic metastases, for treatment planning, for interventional image-guided procedures, and for post-treatment evaluation [57]. MRgHIFU requires additional MRI sequence protocols, compared to general diagnostic MRI.

4.1 Diagnostic MRI for CRLM

Although CRLM is usually confirmed with computed tomography, MRI is an acceptable and common alternative, and is advantageous at identifying small lesions [1]. Some studies have shown MRI to provide the best results among all diagnostic imaging modalities, though more expensive [58]. The primary objectives for MRI liver tumor diagnosis are to verify the neoplasm presence, staging the lesion, and

classifying the type of neoplasm [22]. Accurate assessment of these techniques is crucial to guiding subsequent treatment such as resection, biopsy, and chemotherapy [22]. National Comprehensive Cancer Network (NCCN) guidelines recommend CT be used for initial workup and staging; with MRI recommended for potentially resectable cases, prior to locoregional treatment, and for inadequate imaging with CT [59].

Metastatic liver tumors have been reported as a factor of 18–40 more frequent than primary tumors [17]. The presence of both benign and malignant liver lesions are common. The challenge is often distinguishing the benign liver lesions from malignant lesions, as misdiagnosis can greatly impact staging and treatment planning. CRLM lesions exhibit T_1 signal hypointensity, higher FATSAT-T_2W signal intensity, and higher diffusion-weighted imaging (DWI) signal intensity. On T_2W, the tumor resembles a target; with coagulative necrosis causing a relatively higher signal intensity in the tumor center, followed by a reduced signal exterior due to bulk desmoplasia, and an even lower intensity thin edge from desmoplasia growing at the periphery. This thin edge resembles a ring in the arterial phase when gadolinium is administered. These features can change due to fatty liver infiltration and edema [60].

Standard liver tumor protocols are concerned with imaging the parenchyma, vascular supply, and biliary tract [61]. Basic liver protocols often include: T_2 half acquisition single-shot turbo spin echo (HASTE) localizer, in-op phase T_1 Gradient Recall Echo (GRE), T_2 fast spin echo (FSE) with fat saturation (FATSAT), and gadolinium-enhanced 3D FATSAT T_1 GRE [61, 62]. The HASTE localizer uses a motion insensitive T_2 single-shot spin echo sequence in combination with half-Fourier to acquire a multislice image in about 2 seconds during a single breath hold [63]. The in-op phase Dixon technique, is a spectroscopic technique used to suppress fat signal, quantify the hepatic fat content of the liver, and estimate iron content [63]. The spectroscopic method distinguishes an image at the $-CH_2$ fat chemical shift from an image at the water chemical shift [64]. In-phase and op-phase sequences are often spin-echo or GRE sequences with equal repetition times, but different echo times. It acquires a normal in-phase image containing the water and fat, an opposed-phase image containing the water phase signal lessened by the fat phase contribution. Combining in-phase and op-phase images generates the water only image, and subtraction of the op-phase image from the in-phase image allows isolation of the fat signal [64, 65]. Additionally, the Dixon technique allows the generation of a T_2^* map, from which the local iron content (mg g^{-1}) can be formulated [65, 66].

Of high importance in clinical diagnosis of liver lesions are DWI and hepatocyte-specific magnetic resonance contrast agent imaging, with MRI elastography to a lesser extent [67]. DWI is particularly useful for detection of small metastatic lesions [61]. Liver DWI consists of a T_2 sequence with symmetric diffusion sensitizing gradients centered on the 180° refocusing pulse [67, 68]. Brownian motion of water molecules is more restricted in tumors and provides a noticeable degree of contrast compared to normal tissue [69]. The DWI sequence is generally used without the administration of a contrast agent, making it a completely non-invasive diagnostic sequence. The weighting factor in DWI is adjusted based on the b-value, that is a function of gradient strength and duration. The apparent diffusion coefficient (ADC) maps can be viewed by removing the T_2-weighting from a series of diffusion-weighted images. Hyperintense regions generally correspond to regions of low fluid diffusion [63].

CRLM lesions are a solid liver lesion and a general protocol for identification and characterization can be described as follows. First, a highly T_2-weighted SSTSE to identify benign fluid-filled lesions, such as cysts and hemangiomas. Next, a modestly T_2-weighted FATSAT-TSE or DWI to identify metastatic tumor sites. Then, a Dixon

sequence might be used to observe the degree of fat infiltration into the tumor. Lastly, a contrast-enhanced image can be used for T_1-weighted phase imaging to characterize the tumor [70].

Extracellular gadolinium agents are the most common contrast agents for general imaging throughout the body [71]. Two common hepatic specific contrast agents are gadoxetate disodium (Gd-EOB-DTPA, Primovist, Eovist, Bayer Healthcare Pharmaceuticals) and gadobenate dimeglumine (Gd-BOPTA, Bracco Diagnostics) [67]. In some studies, Gd-EOB-DTPA hepatocyte specific MRI contrast agents has shown improved sensitivity and specificity in diagnosis of liver metastasis compared to computed tomography, particularly to the improved ability to detect small metastases [67, 72]. The hepatic-specific contrast agents are specific to tumors originating from hepatocytes, and can help distinguish these lesions from cavernoma or metastatic lesions [71, 73]. Though, these are more expensive than extracellular analogues, have a lower recommended dose and signal, and can exhibit reduced uptake in patients with hepatocyte dysfunction [69]. A comparison of DWI and Gd-EOB-DTPA-T_1W MRI for detecting small lesions from CRLM are shown in **Figure 1** [74].

4.2 MRgHIFU sequence aspects

MRgHIFU requires additional MRI sequences that allow for temperature mapping. MR temperature mapping most commonly utilizes PRFS thermometry [75–77], though other possible techniques allow temperature measurements based on the temperature-dependence of relaxation rates, proton density, water diffusion coefficient, thermosensitive contrast agents, and magnetization transfer [78, 79]. Resonance frequency shift results from temperature differences in water molecules and aqueous tissues, due to varying degrees of hydrogen bonding. At increased temperatures, the amount of hydrogen bonding is reduced. This increases nuclear shielding of water protons from the incident magnetic field, generating a lower resonance frequency in the water molecules [78]. This results in a linear-dependence of the phase map values from the chemical shift due to temperature change, at a rate of about -0.01 ppm $°C^{-1}$ [78, 79]. MRgHIFU sequences

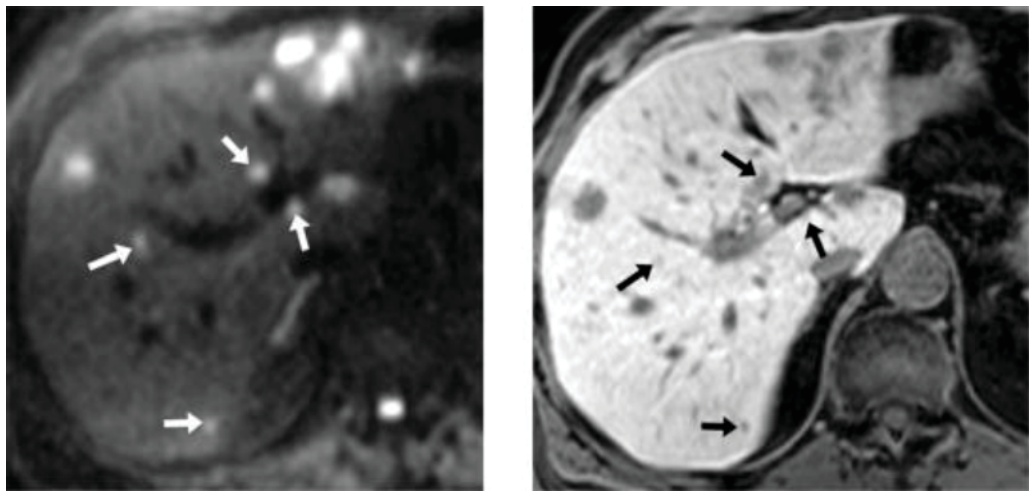

Figure 1.
Comparison of diffusion-weighted MRI with contrast-enhanced T_1W MRI. Left: diffusion-weighted MRI of liver metastases. The arrows indicate small metastatic tumors, less than 1 cm diameter. Right: CE-T_1W image after applying Gd-EOB-DTPA, in the same patient. Reprinted with permission from Koh and Berry [74].

are often based on GRE segmented echo-planar imaging (SEG EPI) sequences. A basic GRE sequence is the fast low-angle shot (FLASH) sequence that utilizes small flip angles to obtain a short echo time (TE) and repetition time (TR) [80]. The sequence further benefits from EPI to accelerate the acquisition rate.

Additional sequences are used to assess tissue peri-ablation and post-ablation. During the peri-ablation period, inflammation in the focal region results from edema, giving more contrast enhancement, and remains for some months. After ablation, T_2 and peripheral T_1 hyperintensity increases significantly due to the presence of hemorrhagic debris at the ablation region. Thickening or nodule formation in the peripheral hyperintense signal can also indicate recurrence or incomplete ablation, during the months following the procedure [67]. Alternative sequences are under study for other aspects of the modality. For example, magnetic resonance acoustic radiation force impulse (MR-ARFI) sequences allow simultaneous displacement and temperature measurements [81, 82], and is implemented in clinical research settings for tracking focal spot and assessing positioning errors [83, 84]. Additionally, MR-ARFI sequences are being studied for phase aberration correction that occurs in transcostal or transcranial procedures [85–87].

Also, thermal ablation needs temperature processing less than about one second. The faster sequences result in reduced signal to noise ratio and increased temperature uncertainty. Echo planar imaging, parallel imaging, alternate trajectories, and undersampling can increase the MRI frame rate [88–90]. In typical rectilinear sampling, the RF pulse frequency and slice-select gradient determine the slice to be imaged, the frequency encoding gradient amplitude controls the k_x-dimension position, and the phase encoding gradient amplitude controls the k_y-dimension position [54]. Alternate trajectories are useful, particularly for fast acquisition times and reducing motion artifacts. Radial trajectories are utilized in some of the fastest real-time MRI sequences [90]. Magnetic field inhomogeneities and magnetic susceptibility are also significant aspects to proper imaging and temperature mapping [91, 92].

5. Surgery for CRLM

Primary colon cancer is classified IV in patients presenting CRLM [2]. Most CRLM patients develop liver metastases after initial CRC treatment, while about 20–34% present liver nodules at initial diagnosis [59]. When CRLM are confined to the liver, the intent should be cure, and surgical resection is actually the standard of care, presenting the best survival rates [59, 93]. Neoadjuvant and adjuvant systemic therapy are recommended in most patients prior to surgical resection, as it can improve instances of recurrence [1, 59]. The response to neoadjuvant chemotherapy has shown to be a strong prognostic factor for outcomes after hepatic resection [94]. The aim of liver resection is to remove all macroscopic disease with clear (negative) margins and leave sufficient functioning liver, with proper vascular and biliary flow [95]. An inadequate future liver remnant volume (FLRV) can lead to post-hepatectomy liver failure, a major cause of morbidity and mortality. Typically, FLRV is intended to be more than 30% of the native tissue and 30% future liver remnant, or more than 350 grams of liver remaining per 70 kg body weight [1]. The anatomic description of functional segments, which is based on the organ's blood supply via the hepatic artery and portal vein, its venous drainage via the hepatic veins, and lastly its biliary drainage, is the foundation of liver surgery. Historically, up to six Couinaud segments can be removed in healthy individuals, returning to original size in about three weeks,

with restored liver function in about six weeks [29, 96]. An illustration of the liver segments are given in **Figure 2**.

Typical resection complications occur in 20–50% of patients, although the mortality rate is only 1–3% in high volume centers [29, 97]. Most common complications include pleural effusion or pulmonary atelectasis, venous catheter infection, site-incisional infection, ascites, subphrenic infection, intraperitoneal bleeding, biliary tract hemorrhage, coagulation disorders, and bile leakage [98]. Additionally, inadequate post-operative liver response can result from pre-operative liver dysfunction, prolonged vascular occlusion, and inadequate resid-ual liver volume; leading to hepatic insufficiency that results in ascites, mental impairment, hyperbilirubinaemia, and possible sepsis [98]. Post-operative liver function can be evaluated by dynamic functional testing such as indocyanine green (ICG) clearance rate, or by aminopyrine breath tests for cytochrome P-450 function, and post-treatment monitoring with blood serum tests for analytes including coagulation products and albumin [98].

Surgical resection for synchronous CRLM is an extremely complex scenario and surgery remains one of the major curative treatment options available.

Consideration for surgical resection must be given to: the anatomical distribution of the disease; FRLV; management of the primary disease (in the setting of synchronous CRLM); the timing and role of (neo)adjuvant chemotherapy, and whether all disease can be resected successfully at one sitting. Patients are often administered chemotherapy and chosen to undergo a conventional colon-first procedure, a liver-first procedure, or simultaneous resection [99]. Even for patients presenting multifocal bilateral CRLM, the goal should be a full tumor excision with sufficient remaining functional parenchyma. Though, for multifocal bilateral CRLM, resection and ablation often yield survival rates only faintly superior to chemotherapy alone [99]. The traditional colon-first approach involves complete primary CRC tumor resection, along with systemic chemotherapy, then hepatectomy is performed later if resectable [100]. A "liver-first" approach involves

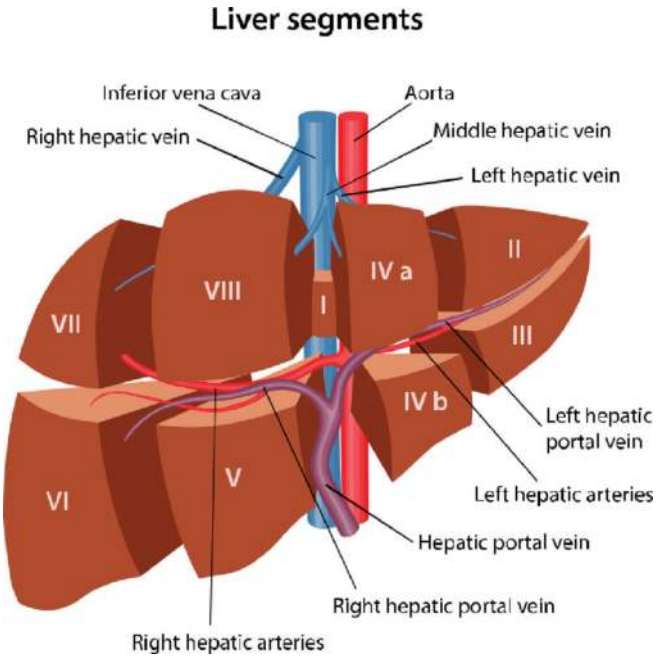

Figure 2.
Illustration identifying locations of individual Couinaud segments. Olga Bolbot/shutterstock.com.

initial systemic chemotherapy, liver tumor removal, then CRC resection [100]. The concept is that the liver tumor is most likely to create further metastasis and the CRC is quite sensitive to systemic chemotherapy [101]. With either approach, approximately only 10–20% of patients are surgical candidates [2, 8, 102]. Reasons include late-stage cancer diagnosis, secondary tumor sites outside the liver, and existing comorbidity ineligibility [2, 8]. Although surgical resections report long-term survival rates, about half of the patients develop widespread metastases within three years [1]. Recurrence after primary liver resection occurs at about a 43% rate in the liver and about a 31% rate in the lungs [8].

Anatomic resections usually involve two or more hepatic segments, while non-anatomic resection involves resection of the metastases with a margin of uninvolved tissue (segmentectomy). Various approaches in liver resection include: right hepatectomy, right lobectomy, left hepatectomy left lobectomy, extended right hepatectomy, and extended left hepatectomy [103]. By performing a segment-based resection, intraoperative hemorrhage and remaining post-treatment ischemic tissue can be avoided, helping to prevent infection and bile duct fistula. Additionally, the segment-based approach allows predetermined calculation of tumor margins and remaining viable parenchyma. Moreover, intrahepatic metastases tend to arise in the same Couinaud segments, allowing better chances to remove small satellite metastatic sites [103, 104].

Modern surgery resection is based on the report of the first successful proce-dure for a right hepatectomy [103, 105]. An illustration of the basic liver anatomy is shown in **Figure 3**. Each Couinaud segment is functionally independent, receiving blood supply from the portal vein and from the hepatic artery; at the same time the outflows is guaranteed by various branches of the hepatic vein. The right hepatic lobe is composed of Couinaud segments 5–8, with the blood supply to the right lobe provided by the right portal vein and right hepatic artery. First, the falciform ligament, coronary ligament, and right triangular ligament are cut to allow increased liver movement. Next, the right hepatic artery, right portal vein, right hepatic duct, and cystic duct are clamped, cut, and ligated. The blood supply to the left lobe is kept intact. This is followed by dissection of the right lobe from the inferior vena cava. Venous outflow from the main and short hepatic veins are divided and ligated. This devascularization creates a line of demarcation due to a color change in the right liver lobe. Then,

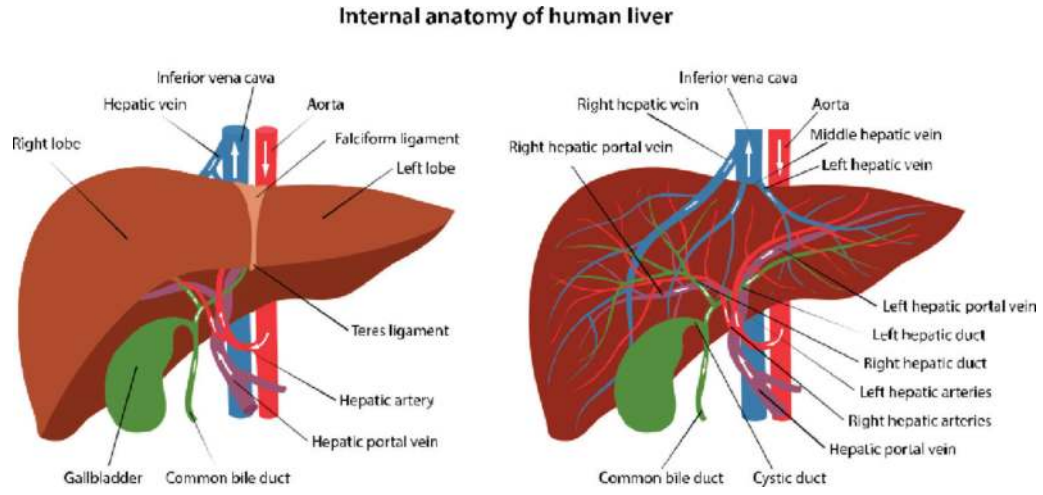

Figure 3.
Overview of the liver anatomy. Olga Bolbot/shutterstock.com.

transection of the liver parenchyma occurs, dividing the right and left lobes along the middle hepatic vein. This is followed by ligation of the middle hepatic vein blood supply. Parenchyma transection can result in large blood loss that can be lessened using a reduced central venous pressure and Pringle's manoeuvre [103, 104, 106]. Three major complications for the procedure include the introduction of an air embolism into the hepatic veins, hemorrhagic bleeding from the hepatic veins, and biliary leakage into the abdominal cavity [107].

The concept of the "two-staged hepatectomy" has been introduced by Adam et al. [108], as a surgical strategy that could be applied to patients with conventionally irresectable metastases to make them eligible for liver resection. This approach involved a combination of systemic chemotherapy to downstage tumors, with or without portal vein embolization (PVE), with subsequent planned staged operations that permitted curative resection of large tumor burden that would otherwise have been considered unresectable. The interval between operations enabled hypertrophy of the remnant liver to theoretically reduce the chance of liver insufficiency and patients would receive chemotherapy during the interval between operations in an effort to control tumor growth.

More recently, the technique known as ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) allows removal of extensive tumor load by increasing future liver remnant, allowing increased surgical eligibility, and extended survivability of CRLM patients [109, 110]. Early research included right PVE, which was shown to induce hypertrophy in the left lobe, subsequently allowing increased amounts of liver tissue to be removed in the right lobe [108, 110–112]. This was later applied in two-stage hepatectomies to allow increased amounts of cancerous liver tissue to be removed from both liver lobes, by permitting liver regrowth between procedures [110]. Early two-stage hepatectomies required months for liver regrowth, with tumor progression frequently occurring during this time; however, development of ALPPS allowed the two surgical procedures to be performed within 7–14 days [109, 110]. ALPPS is indicated in case of extensive multifocal CRLM, failure after portal vein embolization, and expected small amounts of FLRV [14].

A generic procedure for two-stage hepatectomy of left lobe wedge resection combined with right lobe hepatectomy includes in situ liver splitting in addition to portal vein ligation [113]. First, the falciform ligament is cut, then tumors locations are confirmed and marked by intraoperative ultrasound. The transection line(s) is identified. Then, the right cystic duct and artery are ligated, followed by dissection and ligation of the right portal vein at the portal bifurcation. The right and middle hepatic veins are isolated, the space between is dissected, and umbilical tape is placed for the hanging maneuver. Then, transection of the parenchyma is performed at the site previously marked with/without Pringle maneuver. The liver is patched, drains placed, abdomen closed, ending the first stage. At this stage the liver is separated but not removed. Then, functional liver testing and weekly volumetry measurements are performed with CT or MRI until the future liver remnant volume surpasses 30%. In the second stage, the incision is reopened, and the hepatic artery and bile duct are ligated on the right lobe that previously underwent portal vein ligation. Then, transection of the right hepatic vein is followed by removal of the right liver lobe and closure of the abdomen.

In the last decade, it has been conceptualized that liver transplantation could offer the theoretical advantage of a real R0 resection, removing also all potentially undetected metastases. Earlier studies in American and European populations showed that transplant after non-neuroendocrine liver metastases from various primary

sites yielded one-year survival rates of only 5%, which is compounded by the lack of available donors [33]. More recent studies with tightened inclusion criteria have shown more favorable outcomes and resulted in a large increase in CRLM transplants worldwide [30, 31, 114]. The studies have suggested much longer survival rates after liver transplant for CRLM, when the inclusion criteria included adequate response to chemotherapy, excised primary tumor sites, more than one year between diagnosis and transplant, and liver only metastases [31, 32, 115]. Additional exclusion criteria exist based upon molecular profiling; for instance, exclusion is recommended due to V600 BRAF mutations and MSI from DNA mismatch repair (MMR) mutations [116]. These results have suggested liver transplant possibly provides the best overall survivability compared to other treatment modalities for surgical ineligibility. The drawbacks are smaller study size, the limited availability of liver donors and more specialized training is required across multiple disciplines to conduct the operation [30].

6. Chemotherapy for CRLM

Systemic chemotherapy in CRLM is administered to attain surgical eligibility, for disease control, peri-operatively, or palliatively; since the treatment alone is rarely curative, with 5-year survival rates less than 10%, and historically less than 1% [25, 30, 117]. Polymetastatic liver disease faces treatment limitations with chemotherapy being the primary treatment. The survival rate is poor and a large demand exists for improved treatment options. As surgical resection offers the best long-term survival rates, the aim of systemic chemotherapy is often to downsize tumors to convert ineligible patients to surgical candidates, with systematic review showing a conversion rate for R0 resection in initially ineligible patients at 23% [118]. Chemotherapy regimens are administered neoadjuvantly prior to hepatectomy for cytoreduction, to reduce metastatic tumor size, allowing smaller resection volumes [119]. The regimens are also administered after resection to reduce recurrence [25, 120]. Hepatic intra-arterial infusion is often beneficial because the liver metastasis is supplied by the hepatic artery network, normal tissue is supplied by the portal vein, and locoregional treatment can be performed without exposing much healthy tissue [121–123]. The liver contains a capillary network of sinusoids that filter the blood as shown in **Figure 4**. Approximately 45% of metastatic tumor cells, predominately arriving from the hepatic arterial network [123], become embedded in the sinusoids [89]. Normal liver parenchyma receive about 80% of the blood supply from the portal vein and about 20% from the hepatic artery. In contrast, about 80% of the tumor blood supply arrives from the hepatic artery [116]. This allows locoregional embolization techniques, like radioembolization and chemoembolization, to both embolize the blood supply to specific tumor segments, and deliver locoregional radiotherapy or chemotherapy. These embolization techniques are suggested to be considered for metastatic CRC limited only to the liver, and after unsuccessful chemotherapy [1].

The chemotherapy regimen depends on a number of factors, including: aim of cytoreduction prior to surgery, aim of disease control, aim of palliation, type of somatic gene mutation, and wild-type or mutant phenotype. Somatic mutations of RAS proto-oncogenes have been found in up to 52% of CRLM hepatic resections, with up to 6–12% of resections expressing BRAF mutations, and co-occurring proto-oncogene RAS and TP53 tumor-suppressor mutations as common genetic events [1, 94]. According to ESMO guidelines, first-line chemotherapy for cytoreduction in RAS

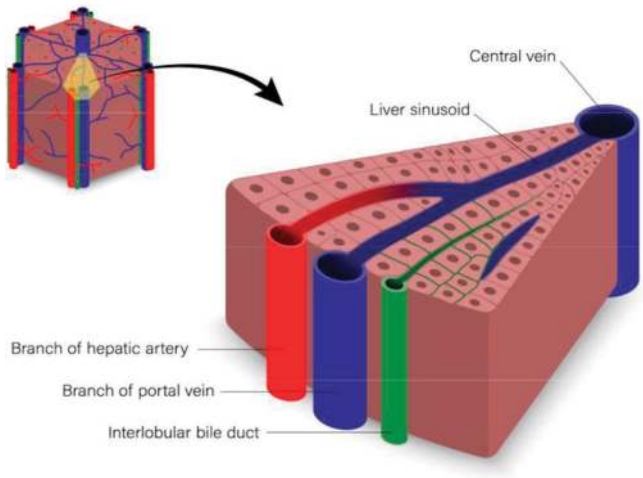

Figure 4.
Histological depiction of liver lobules. These units are microscale components of liver tissue. The liver sinusoids are small capillaries, with blood supplied by small branches of the hepatic artery and portal vein. Deesign/shutterstock.com.

tumors should be recommended cytotoxic doublets (FOLFOX/CAPOX/FOLFIRI), in combination with VEGF antibody bevacizumab for RAS mutant-type tumors, and EGFR antibodies for wild-type tumors. FOLFOXIRI with bevacizumab are recommended as a first line treatment for cytoreduction in CRLM BRAF mutant tumors [1].

Chemotherapeutics can also exhibit many adverse side-effects on healthy liver tissue. Side-effects include sinusoidal obstruction syndrome and chemotherapy-associated steatohepatitis, that can lead to liver failure or increased mortality rates [119]. Additionally, the chemotherapy can cause missing metastases, making lesions unidentifiable on radiological imaging, complicating surgical decisions, and increasing the chance of recurrence [119]. Chemotherapy has difficulty supplying tumor cells with adequate drug dose. The maximum dose is limited by systemic toxicity effects and inadequate tumor penetration is common [8, 124]. Intrahepatic arterial delivery can exhibit acute side-effects of hepatocellular atrophy causing cirrhosis and necrosis [123, 125].

Doxorubicin is an anthracycline chemotherapeutic that can be administered during combination therapy. A liposomal form was created relatively early due to the need for better treatment in Kaposi sarcoma from autoimmune deficiency syndrome [126]. Clinical trials of FUS-mediated thermosensitive liposomal doxorubicin drug delivery to liver tumors [127, 128] have shown large increases in intratumoral doxorubicin concentration, and there are ongoing trials with MRgHIFU for pediatric tumors [129]. Similar ongoing trials are studying the enhanced ability for microbubbles to improve chemotherapy delivery to metastatic liver tumors [130].

7. Radiotherapy for CRLM

Radiotherapy emits ionizing radiation at tumors, causing DNA damage, and apoptosis. The technique exhibits some similar drawbacks to focused ultrasound. Cumulative radiation exposure can occur in the beam's near and far field, resulting in unwanted tissue damage [8, 131, 132]. Also, systems require computed tomography

guidance and respiratory motion control [8, 133]. Local ablative techniques, including radiotherapy, are generally considered to be limited to patients with unresectable CRLM or oligometastatic disease [1]. CRLM radiotherapy has often been limited by liver parenchyma radio-sensitivity. External beam radiation doses of 70–90 Gy needed for CRLM and HCC tumor treatment exceeds tolerance limits of 35 Gy for radiation-induced liver disease (RILD) [57, 134] that can lead to liver failure and death [25]. The condition occurs two to sixteen weeks after treatment, is identified by ascites, high levels of alkaline phosphatases, and high levels of liver transaminases [135].

Stereotactic body radiation therapy (SBRT) with linear accelerators has recently gained much interest for surgical ineligibility, particularly in oligometastatic disease. With SBRT, fiducial markers are percutaneously placed near the tumor site to allow precise tumor targeting [57]. Though MRI guidance reduces invasiveness, without the need for fiducial markers [116]. SBRT is recommended by ESMO to be considered for patients with oligometastatic disease who are ineligible for surgery and ablative therapy [1]. One major advantage of SBRT compared to ablative therapies is that the treatment is non-thermal, mitigating some of the common side-effects seen in local ablative techniques, such as fluid perfusion effects [116]. Studies have shown that liver failure is infrequent when only a portion of the liver is irradiated [135]. The liver toxicity is mild to moderate, with liver failure in less than 1% of patients [136, 137]. Treatment of oligometastatic CRC in the liver with SBRT, suggests one and two year overall survivability at about 67.1% and 56.5%, respectively [137]. Many early phase clinical trials are recruiting, active, or recently completed, for treatment of primary or secondary hepatic tumors with magnetic resonance guided linear accelerators [138, 139] and magnetic resonance guided SBRT [140–143]. Recent phase I trial results with magnetic resonance guided SBRT, showed improved toxicity, with estimated 2-year overall survival of 51%, and median overall survival of 29 months [144].

8. Focused ultrasound clinical studies for liver cancer

A substantial number of clinical studies, cohorts, and randomized control trials for non-liver MRgHIFU and MRgFUS have been reported, including: treatment with bone osteomas or palliative bone metastasis [145, 146], uterine fibroids [147–151], gynaecological tumor recurrence [152], prostate cancer [153, 154], essential tremor [155, 156], and breast cancer [157]. Many clinical studies have been reported for USgFUS ablation for liver tumors [158–165], with most studies reporting on HCC ablation [166]. Similar to USgFUS, new histotripsy devices using cavitation rather than thermal ablation, are currently being studied for the treatment of primary and secondary tumors, with an active prospective clinical trial [45, 46, 167, 168]. No Phase III trials for USgFUS or MRgHIFU ablation of CRLM have been published [116]. Early USgFUS studies in liver malignancies, not distinguishing between metastatic liver tumors and primary liver tumors, showed a median survival time of 13.4 months, 6-month survival times of 82.6%, and 12-month survival time of 53.4% [159]. More recent systematic reviews of FUS for liver malignancies have given 1 year, 2 year, and 5-year survivability of 81%, 60%, and 39%, respectively [166]. Most studies have been conducted using the Chongqing Haifu JC system, capable of up to 300 W acoustic power and peak intensity up to 20,000 W cm^2 [166]. The system has received the mark Conformite´ Europeenne´ (CE), being the most reported system for clinical liver tumor ablation [2, 3]. The permission is granted to individual commercial models rather than general treatment procedures. The magnetic resonance guided

systems that have received regulatory approval for alternative treatments include the ArcBlate (Episonica, Hsinchu, Taiwan), Exablate (Insightec, Tirat Carmel, Israel), and Sonalleve (Profound Medical, Mississauga, Canada) systems.

Local ablative techniques, including focused ultrasound ablation, are generally recommended only in cases of unresectable liver metastases or oligometastatic disease [1]. Most FUS ablation therapy studies for liver tumors are USgFUS for HCC, with less reports of metastatic liver tumor treatment [166]. Particularly advantageous in FUS is the improved side effect profile and reduced morbidity compared to standard treatment options. The treatment can occur multiple times with no cumulative radiation-like side effects. In relation to chemotherapy, it is much more focused, with less toxicity to healthy tissues [8, 169]. Additionally, extracorporeal FUS liver ablation is completely non-invasive and offers very fast recovery times [170]. Benefits of MRgHIFU compared to USgFUS include near real-time temperature mapping, integration into existing imaging systems, less propensity for radiofrequency interference in the imaging system, and capability of assessing treatment response during the procedure. Though ultrasound-guided devices do not provide real-time temperature map-ping, assessment of grey-scale change are indicative of coagulative necrosis [166]. Treatment plans with FUS generally depend on the cancer staging. Curative ablation of early stage tumors often include a 1.5–2.0 cm peripheral tissue margin. The treatment is administered palliatively for late-stage tumors to slow progression or alleviate symptoms [8, 160].

Drawbacks to hepatobiliary focused ultrasound studies have been the need for general anesthesia, long treatment times, scattering by the thoracic cage, high power requirements, respiratory motion, skin burns, osteonecrosis, skin pain, skin edema, rib resection, fever, the need for intrapleural effusion, and reduced thermal dose from fluid perfusion of surrounding vessels [2, 39, 165, 166, 170–177]. A systematic review of USgFUS for the treatment of malignant hepatobiliary tumors indicated the primary complications were skin burns in 15% of cases, followed by localized pain in 5%, then fever at 2% [166]. Major post-treatment complications include fluid and/or air accumulation in the lungs, biliary obstruction, and fistula occurrence [177].

Some studies have reported focused ultrasound ablation in primary and secondary liver tumors in difficult locations, including near major hepatic veins and arteries, and near surrounding organs of the heart, gallbladder, stomach, and intestine [162, 165, 178]. Tumors located near surrounding organs are high-risk. Particularly sensitive are the bowel and gallbladder due to the thin walls and risks of peritonitis [162].

Skin and rib burns have been addressed in a variety of manners. Skin burns have been reported to occur with tumors located near the subcapsular area, resulting from possible rib reflection or reflections from internal gas pockets in the bowel or lung parenchyma [166]. The right lobe is more susceptible as it is predominately located behind the ribs [162]. Intrapleural effusion can distance the tumor site from the subcapsular area, or rib resection can be performed [162, 179]. Particularly troublesome are tumors of the liver dome in Couinaud segments 7 and 8, due to the close proximity to the lungs, the close proximity to the ribs, and that this region tends to remain behind the rib cage under general anesthesia due to reduced respiration [162]. A small cohort for USgFUS reported that proper intraoperative assessment of the soft tissue prevented skin burns in all patients [161].

A variety of techniques have been tested to overcome respiratory motion and rib interaction. Respiratory motion creates complications requiring organ image

registration techniques [180] and MRI motion artifact compensation [174, 181]. Numerous preclinical studies have undertaken new technologies to address respiratory motion and rib interactions [39, 172, 174–176, 180, 182–186]. Previous USgFUS human studies have generally been successful at performing ablation through the ribs; though additional measures have included left lung ventilation with endotracheal intubation and general anesthesia to reduce liver movement, intrapleural effusion, and rib resection [160, 162, 179]. MRgHIFU pilot studies used intermittent sonications, and limited to the treatment to the left liver lobe, in tumor sites not blocked by the ribs [170, 187–189].

Handheld intraoperative HIFU devices under ultrasound-guidance are in development, and being tested in early phase clinical trials for CRLM tumor abla-tion. The technique is similar to intraoperative radiofrequency and microwave ablation, but prevents the need for an intraparenchymal probe. Results have been reported using the device for ablating tissue near tumors in segments prior to surgical resection, to assess accuracy and safety. Applications include reduction of hemorrhaging during surgery and potentially bridging more patients for surgical resection [190–193]. The device was shown capable of in vivo hepatic vessel occlusion for diameters of 2 mm [194], and studies have reported diameters of left hepatic arteries and right hepatic veins between 3 and 4 mm [195].

Several small clinical studies have been reported for MRgHIFU ablation for HCC [170, 187–189, 196, 197]. There is currently an ongoing Phase I clinical trial with MRgHIFU for a variety of pediatric solid tumors, in which hepatic tumors are eligible [198].

In the study from Okada et al. [187], MRgHIFU liver tumor ablation was performed on a single patient. The MRI system utilized respiratory gating and ablation was performed on a 15 mm HCC lesion. The procedure required about two hours to ensure complete coagulation by repeated coverage. Gadolinium contrast agent was administered post-treatment and no increased signal intensity was observed at the tumor site, indicating expected ablation contrast. The authors noted the need for better technology for avoiding bowel loops, ribs, and respiratory liver motion. Though, the patient only complained of slight skin heating discomfort during treatment and was released from the hospital the following day.

Anzidei et al. treated a single HCC patient more comprehensively with MR-FUS [188]. The patient refused surgery and percutaneous ablation, then opted for MR-FUS. The individual had no distant metastases, was treated successfully, and later underwent total liver transplant. Excised liver histopathology showed complete coagulative necrosis with only slight recurrence at the ablation periphery. The investigators noted the procedure can be improved with better respiratory motion control and expected that future applications would use automated feedback algorithms.

Gedroyc conducted a series of pilot studies for MRgHIFU liver tumor ablation [170, 189]. It was reported that the absorption from the ribs was problematic and the treatments were limited to patients with exposed tumor sites, such as below the rib line or in the left lobe of the liver. One case was a female with HCC arising from Hepatitis-B infection. She was previously treated with hepatic arterial chemoembolization and laser ablation. Recurrence occurred with a 1.5 cm HCC lesion in the left lobe within Couinaud segment 3, a position that was not covered by the ribs. The site was ablated with MRgHIFU. In another case, the patient was a male with HCC, Hepatitis-C, extensive cirrhosis, and elevated alpha-fetoprotein levels. He was treated for a 3 cm HCC in the anterior portion of the left liver lobe.

9. Conclusions

Optimal treatment strategies for CRLM patients should be made by a multidisciplinary team as part of a tumor board, for establishing diagnostic and treatment strategies [1]. Surgery of CRLM will likely provide the best long-term outcomes and the strategy should focus on complete resection. Although, the majority of patients with CRLM are ineligible for surgery and many surgical cases will experience widespread recurrence. Thermal ablation methods like focused ultrasound are generally only recommended for unresectable CRLM and oligometastatic disease, with at least one system under ultrasound guidance having the CE-mark for CRLM [1, 2]. Due to expected increasing CRLM incidence and high surgical ineligibility, non-invasive technologies like MRgHIFU systems have great potential for clinical translation as an ablative interventional radiology procedure.

Guidelines for FUS pilot studies suggest performing MRgHIFU ablation in CRLM patients prior to the surgical operation, then surgically removing the ablated tumor, and assessing the effectiveness with pathology [2]. Randomized control trials have been suggested to be performed on CRLM patients that are not candidates for surgical resection or RF ablation, and to compare TACE and MRgHIFU to a control group receiving only TACE [2]. In a randomized controlled trial, USgFUS for primary liver tumors in combination with TACE has shown improved treatment over TACE alone, increasing survival times, giving higher remission rates, lower recurrence rates, lower rates of post-operative metastases, and less instances of hemorrhaging in the digestive tract [199, 200].

MRgHIFU has been established in proof-of-concept studies for HCC, limited to the left liver lobe or section not covered by the ribs, requiring intermittent ablation due to respiration, and has not been reported in randomized controlled trials for primary or secondary liver tumors [170, 187–189, 196, 197, 201]. The FUS field has gained much interest in recent years and MRgHIFU ablation of primary and secondary liver tumors appears likely to begin early phase trials in the near future. Previous focused ultrasound studies have developed methods to address many technical complications such as respiratory motion and suppressing prefocal interactions; with focusing through the ribs being one of the major technical difficulties. Long treatment times are another complication and should improve with automated feedback control and faster acquisition times.

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