Ablative Techniques for CRLM: Alone or in Association

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Introduction

Approximately half of the patients diagnosed with colon cancer will suffer from colorectal liver metastasis (CRLM) during their management. Currently, the standard treatment for hepatic metastasis is surgical resection with a potential curative intent. When surgery is not feasible, patients may undergo systemic treatment to downstage lesions and allow them to become eligible surgical candidates. Despite improved systemic therapies, surgical techniques, and perioperative care, most of the patients still remain ineligible for surgical resection and hence the reason for alternative techniques for local control of the disease.

Ablative techniques for the treatment of CRLM offer a less invasive treatment route than hepatic resection and can be used alone or in association with resection and/or chemotherapy.

In general, ablative techniques for CRLM can be divided into thermal and nonthermal techniques. Thermal techniques rely on differing mechanisms of delivering energy to the tumor site in order to increase or decrease local temperatures to cytotoxic levels. Thermal techniques examined in this chapter include laser-induced thermotherapy (LITT), high-intensity focused ultrasound ablation (HIFU), radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation. In techniques using thermal energy to increase tissue temperature, energy loss may occur due to local blood flow. This heat-sink effect is more pronounced in tumors located near major blood vessels [1]. Cryoablation, on the other hand, uses the opposite effect—quickly lowering temperatures to cytotoxic levels.

Nonthermal techniques that will be reviewed include chemoablation, which refers to ethanol or acetic acid ablation; irreversible electroporation (IRE) which uses electrical current to irreversibly damage the cell membrane causing cellular

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Table 36.1 Classification of liver ablative techniques by method of action

Liver ablation techniques
Thermal techniques
Coagulatives
Laser-induced thermotherapy (LITT)
High-intensity focused ultrasound ablation (HIFU)
Radiofrequency ablation (RFA)
Microwave ablation (MWA)
Cryoablation
Nonthermal techniques
Chemical ablation
Ethanol injection
Acetic acid
Irreversible electrophoresis (IRE)
Stereotactic body radiation therapy (SBRT)

apoptosis; and stereotactic body radiation therapy. See Table 36.1 for classification of ablative techniques by method of action.

This chapter will focus on describing current available ablative techniques in the treatment of CRLM and will discuss the evidence of outcomes when used alone or in association with other techniques.

Types of Ablative Techniques

Thermal Techniques

Laser-Induced Thermotherapy (LITT)

- LITT requires laser fibers to be inserted into target tissue.
- Ablation size is limited to 1–1.5 cm unless multiple-applicator arrays are used.
- Usually well tolerated with low risk of major complications.

LITT, also known as laser ablation, requires laser fibers to be inserted into the target tissue. LITT systems usually consist of a generator connected to a neodymium:yttrium aluminum garnet diode laser (wavelength of 1064 nm) [2]. The light energy from the fiberoptic applicator tip is absorbed by the target tissue and converted into heat when the photons are absorbed by naturally occurring chromophores [2, 3]. This heat is used to increase tissue temperatures to cytotoxic levels. Charred and desiccated tissue limits penetration of the photons, limiting ablation size in LITT to 1–1.5 cm. Slow heating and multiple-applicator arrays can be used to address this limitation and increase ablation zone size limitations [2].

The benefits of LITT closely resemble those of other thermal ablative techniques. It can be combined with resection to minimize the extent of resection required [4]. One early study from 2003 examined the use of transarterial chemoembolization (TACE) to downsize unresectable hepatic tumors prior to MRI-guided LITT. It was

found that TACE combined with LITT produced significantly better median survival than TACE alone (26.2 and 12.8 months, respectively) [5].

According to Knavel et al., one major benefit of LITT over other ablative techniques is that most LITT systems are MRI compatible, allowing for intraprocedural temperature monitoring, though the authors do acknowledge the increased cost and limited availability of these options [3].

The major complication rate of LITT is acceptably low, with reported rates of 0.1–3.5% [4].

Originally, the intention of LITT was limited to palliative control of CRLM, but survival data have shown that it is comparable to resection in survival rates with decreased morbidity and mortality in selected cases [4]. As with other ablative techniques, Vogl et al. found that the number and size of tumors were significant prognostic indicators of overall and progression free survival (PFS) in patients treated with LITT. Median survival in 594 patients with CRLM was 25 months and median PFS was 13 months [6]. A recent review reported median survival ranging from 14.8–54 months, though combined median survival from all studies examined was 33.7 months [4].

A prospective study of 44 patients published in 2006 by Pacella et al. analyzed percutaneous LITT for treatment of unresectable CRLM. The authors found an overall survival of 30.0 ± 12.7 months in patients with complete ablation and no major complications during the study. Incomplete tumor ablation was associated with a significantly lower overall survival (20.2 ± 10.2 months). Tumor diameter <3 cm was a strong predictor of complete ablation [7]. However, more robust data are lacking. According to a review of available and future ablative techniques by Facciorusso et al. from 2016, the limited availability of LITT data limits its use until it can be further studied [8].

High-Intensity Focused Ultrasound Ablation (HIFU)

- HIFU is a noninvasive technique.
- Better to use on superficial tumors rather than deep ones.

HIFU is a completely noninvasive technique. HIFU uses a transducer to generate ultrasound waves like those used in diagnostic ultrasound imaging, but with increased intensity (720 mW/cm^2 diagnostic vs. 100–10,000 W/cm^2 HIFU) [9]. The ablative effect of HIFU is a result of heat generation from the conversion of acoustic energy into thermal energy, but some cavitation collapse sends shock waves into surrounding tissue as well [3, 10]. HIFU devices focus the ultrasound waves on a focal point. This focus and the rapid increase in temperature helps preserve tissue that is between the focal point and the transducer from thermal damage. Temperatures at the focal point reach 60 °C rapidly and coagulative necrosis occurs within a few seconds [10]. HIFU is limited by ultrasound penetrance and thermal energy that may build up along the path of travel—thus, superficial tumors are better candidates for HIFU ablation than deeper areas of disease [3].

The obvious benefit of HIFU compared to other ablative techniques is its noninvasive status. Additionally, there are both ultrasound- and MRI-guided systems available for intraoperative assessment of treatment [9]. Investigations into the use of HIFU for CRLM were lacking in the current literature, but recent studies of HIFU treatment of hepatocellular carcinoma can give some indication of its potential. A study conducted by Zhang et al. in 2009 demonstrated that hepatocellular carcinoma tumors adjacent to major blood vessels could be safely and completely ablated by HIFU with no major blood vessel injury observed on follow-up in 39 patients (median follow-up 23.8 ± 17.2 months) [11].

A study of 50 patients by Wu et al. found that HIFU could be safely combined with TACE and provided survival benefits (combined therapy median survival: 11.3 months, TACE only: 4 months) in the treatment of advanced-stage hepatocellular carcinoma [12].

Studies into the risks of HIFU have shown that the ultrasound waves can reflect or scatter, causing thermal damage to nearby structures. Skin burns, peripheral nerve damage, bowel injury, and pleural effusion have all been documented [13–16]. Further study of this technique to assess its safety and efficacy is needed.

A phase I-IIa clinical trial conducted in France examining HIFU safety and efficacy for CRLM showed promising results, with 30 ablations in 15 patients causing no damage to neighboring tissue and conducted with a precision of 1–2 mm [17].

Radiofrequency Ablation (RFA)

- RFA requires placement of electrodes which can be done with the guidance of US, CT, or MRI and using laparoscopy, open, or percutaneous approach.
- Usually well tolerated with low complication rates.
- Benefits have been demonstrated when using this technique combined with others and/or surgical resection.
- Higher local tumor recurrence when tumor >3 cm.
- *Use of RFA should be avoided when the target zone is immediately adjacent to vital structures such as the bile duct, major vessels, diaphragm, or bowel due to increased risk of damage.*
- Postablation syndrome present in 1/3 of patients.

RFA is an ablative technique that uses thermal energy derived from the application of electrical current to the targeted tissue. RFA can be performed using open, laparoscopic, or percutaneous approaches. The goal of RFA is complete ablation of the tumor and a surrounding margin [18].

RFA uses alternating current in the range of 450–500 kHz to cause agitation of the ions within the target tissue [19]. Once the resulting frictional heat causes temperatures to reach 60–100 °C, coagulative necrosis occurs due to the irreversible damage to both mitochondrial and cytosolic enzymes within the cells [20]. If temperatures reach 100 °C or above, evaporation causes instantaneous cell death, but the resulting tissue charring by the heated gasses hinders the continued

effectiveness of RFA due to insulating properties of the carbonized tissue [21]. The aim is to achieve temperatures of 50°–100 °C for 4–6 minutes in the entire target volume. Because of the risk of charring and evaporation, slow heating of the target tissue is preferable. Due to the nature of heat conduction in the tissue, this allows a larger target volume to reach desired temperatures [22]. The resulting increase in circuit impedance, thus limiting current flow, is an important limitation on increasing RFA ablative zone size [23].

RFA electrodes (usually 14–21 gauge) are placed directly in the target tissue with the help of imaging such as ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) [24]. A reference electrode in the form of grounding pads is also placed on the patient's skin to disperse heat and prevent cutaneous burns at the pad site [22]. It should be noted that newer systems utilizing a bipolar probe do not require a grounding pad. Because of the low heat conductance of tissue, a single needle electrode has a small effective zone of necrosis. Solutions to this problem include multipronged electrodes, expandable electrodes, interstitial saline cooling, internal cooling of the electrode, and pulsing of the electrical current [25].

RFA shows low complication rates when used to treat cancers of the liver. Koda et al. conducted a multicenter study of the use of RFA to treat hepatocellular carcinoma, which examined 16,346 treated nodules in 13,283 patients, and found a complication rate of 3.5% and a complication-related death rate of just 0.04% [26]. Similar studies of RFA use for liver tumors have reported rates of major complications ranging from 1.9% to 5.7%, with those delineating between CRLM and other hepatic tumors showing similar complication rates for the two diseases [27–31].

RFA can be administered in combination with several other treatment techniques such as traditional resection and chemotherapy. Van Amerongen et al. found that RFA combined with resection to treat CRLM exhibited no increase in morbidity or mortality compared to resection alone and allowed treatment of patients that would have been otherwise considered inoperable [32]. A 2012 study of patients with unresectable CRLM found a significantly increased median PFS time in those treated with RFA plus systemic treatment (16.8 months) compared to those treated with systemic treatment alone (9.9 months) [33]. The investigators continued to publish a 2017 study of the same patients showing increased 3-, 5-, and 8-year overall survival (OS) in those undergoing the combined treatments compared to systemic treatment alone [34]. Chemotherapy can also be used prior to RFA to downstage initially untreatable tumors to a treatable size [35].

Patients with recurrent CRLM may be good candidates for RFA to avoid the technical difficulties of performing reoperative surgery. A study by Valls et al. demonstrated that RFA provides survival benefits in patients with recurrent CRLM of 3 cm or less. Patients with tumors larger than 3 cm experienced a recurrence rate of over 50%, and may be better served with other therapies [36].

However, the risks associated with RFA must be taken into considerations. Local tumor recurrence rates between 18% and 84% have been reported, with other reports varying extensively and are heavily dependent on lesion size [36–40]. A recent study performed by Tanis et al. demonstrated that the local recurrence rate in RFA was comparable to that of resection when tumor size was limited to 3 cm [41].

Postablation syndrome occurs in approximately one-third of patients and is an important consideration for postoperative management [42, 43]. Postablation syndrome manifests as flu-like symptoms, with patients exhibiting malaise, fever, chills, and/or nausea. It is believed that this may be a result of increased cytokine release and immune system activation in response to necrotic tissue [44–46]. Dodd et al. found that lesion size and volume ablated were significant predictors of postablation syndrome [43].

An additional risk consideration for RFA is tumor location. Adjacency to important structures such as the gallbladder or bile ducts, blood vessels, the diaphragm, and the bowel complicate the procedure, making significant bleeding, pleural effusion, bile peritonitis, thrombosis of vessels, and perforation of nonhepatic structures among others a concern [47–51]. Lu et al. found that vessels >3 mm contiguous with the target tumor were a dominant predictor of incomplete tumor destruction or local recurrence. Incomplete destruction or local recurrence occurred at a rate of 7% in the nonperivascular group compared to 48% in the perivascular group [48].

One risk of RFA that seems to have been addressed with newer systems is the risk of superficial burns at the grounding pad site. In order to produce the current used by the electrode, an equal amount of current, and therefore heat, is deposited at the grounding pad site. A review by Rhim et al. notes that second- and third-degree grounding pad site burns are relatively rare when sufficiently large grounding pad area is used [52]. Severe burns can be avoided with careful grounding pad placement [53].

When considered holistically, the benefits and potential of RFA can outweigh the risks. RFA is a safe, well-tolerated procedure that provides alternatives to resection or chemotherapy alone and can be an option for patients whose disease is otherwise inoperable. The recurrence rate, in particular, should be considered however, and candidacy should be evaluated on a case-by-case basis.

The widely accepted ideal size of ≤3 cm is supported by a multitude of studies that show RFA provides comparable survival outcomes to resection alone in tumors of this size [36, 38, 54–57]. A propensity score analysis performed by Lee et al. in 2015 states that survival curves for RFA are comparable to those of resection in tumors ≤2 cm, but asserts that resection provides better outcomes in larger tumors [58]. Two studies conducted by Gillams et al. and Oshowo et al. examined the use of RFA to treat solitary CRLM of up to 5 cm (mean tumor size: 3.9 cm) and 10 cm (mean tumor size: 3 cm), respectively, showed comparable survival outcomes to resection [59, 60]. In addition to tumor size, number of tumors and uncontrolled extrahepatic disease were significant indicators of poorer survivability after RFA [61].

RFA is often conducted as an adjunct to resection and/or systemic chemotherapy. A review conducted by Boame et al. demonstrated that RFA, when used as an adjunct to resection to treat CRLM, does not decrease overall survival [62]. In addition to the studies conducted by Ruers et al. mentioned above, a 2012 study presented data supporting the conclusion that adding RFA to systemic chemotherapy improves overall survival compared to systemic chemotherapy alone [33, 34, 63]. See Table 36.2 for summarizing data of RFA versus liver resection (LR) for CRLM.

Table 36.2 Survival data of RFA versus liver resection (LR) for CRLM

Author	Type of study	Treatment	No. of patients	Morbidity (%)	Mortality (%)	Local recurrence (%)	Median follow-up (months)	Five-year overall survival (%)
Hur et al. [55]	Retrospective	LR	42	14	0	9.5	42	50
		RFA	25	0	0	28		25.5
Otto et al. [64]	Retrospective	LR	82	36.5	0	4	NR	51
		RFA	28	25	0	32		48
Reuter et al. [65]	Retrospective	LR	126	29	NR	2	20	23
		RFA	66	10		17		21
Kim KH et al. [54]	Retrospective	LR	278	21.2	0	NR	NR	51
		RFA	177	6	0			51
Lee et al. [66]	Retrospective	LR	25	4	3.5	8	NR	44
		RFA	28	3.5	0	42.9		17.9
Ko et al. [67]	Retrospective	LR	12	NR	NR	NR	NR	66.7
		RFA	17					37.8

Microwave Ablation (MWA)

- MWA requires placement of electrodes which can be done with the guidance of US, CT, or MRI and using laparoscopy, open or percutaneous approach.
- Faster ablation and less heat-sink effect.
- Usually well tolerated with low complication rates.
- Benefits have been demonstrated when using this technique combined with others and/or surgical resection.

MWA is quite similar in concept and application to RFA, with an electromagnetic wave-producing probe providing energy to heat the target tissue to cytotoxic levels, but does provide some benefits over its predecessor counterpart. A growing body of literature assessing safety, efficacy, and comparisons to RFA has presented several possible advantages to the newer system [3, 68]. The advantages of MWA over RFA and other ablative techniques discussed in this section imply a role for MWA in treatment strategies for CRLM.

The key differences between MWA and RFA systems are the frequency of waves produced and the use of microwaves versus electrical current, respectively. MWA systems generate waves with significantly higher frequencies than RFA, with most systems using either 915 MHz or 2.45 GHz and 45–80 W [69, 70]. Unlike RFA, MWA systems do not need a grounding pad [71]. Microwaves passing through tissue induce oscillation in water molecules acting as dipoles as they attempt to align opposite electromagnetic charges [72]. The oscillation transforms electrical energy

into thermal energy through friction, heating surrounding tissue [18]. Most systems on the market today utilize 14- to 17-gauge antennae with a water or CO_2 active antennae cooling system to reduce unwanted heating around the probe length and prevent skin burns at the site of insertion [3, 71, 73].

Compared to RFA, which relies heavily on thermal conduction for heat dissipation further than a few millimeters from the probe, MWA creates an elliptical field that can reach up to 2 cm from the probe tip, allowing for a larger ablation zones and more uniform coagulative necrosis [72].

Many of the same risks associated with RFA should be considered when employing MWA. Incidental healthy tissue ablation can be avoided with careful application. Skin burns at the site of antennae insertion, though largely avoided by the internal cooling element of today's MWA instruments, can also occur [71]. As a type of thermal ablation, MWA is susceptible to the same heat-sink effect as other thermal modalities [74].

As with RFA, a risk of MWA is local tumor recurrence. Groeschl et al. conducted a multi-institutional analysis of MWA for hepatic malignancies and found a local recurrence rate of 5.2% for CRLM in 393 ablated tumors [75].

MWA is comparable to resection for the treatment of multiple metastases. An early study by Shibata et al. demonstrated that MWA is equally effective as resection for treatment of multiple hepatic metastases while causing a lower amount of intraoperative blood loss (median overall survival of 27 and 25 months, respectively) [76].

Surgical approach for application of MWA in hepatic malignancies—open, laparoscopic, or percutaneous—was examined by Groeschl et al. who found no difference in morbidity or survival between the three in 473 procedures but did find higher rates of local recurrence from percutaneous operations (14.1% vs. 6.0% overall). These recurrence rates were given for all hepatic malignancies, not CRLM specifically. The same study showed median overall survival of patients treated with MWA for CRLM was 32.1 months [75].

MWA as it compares to RFA is of particular interest as the techniques have significant crossover in patient candidacy. A meta-analysis performed by Huo et al. in 2015 examined 16 studies comparing the outcomes of MWA and RFA for hepatic lesions. The investigators found that patients who underwent MWA exhibited a significant increase in 6-year overall survival compared to RFA (odds ratio (OR): 1.64, 95% confidence interval (CI): 1.15–2.35); however, this was based on only 3 of the 16 studies. The same meta-analysis found MWA and RFA comparable in a number of measures including: 1–5-year overall survival, disease-free survival, local recurrence rate, and adverse events [70]. See Table 36.3 for a summary of some important studies into the safety and efficacy of MWA.

Cryoablation

- Cryoablation allows visualization of affected tissue being ablated under US or CT guidance, which helps in monitoring margins.
- Risk of complications is high compared to other hepatic ablation techniques.
- No benefits are seen when associated with other ablative techniques or surgical resection.

Table 36.3 Summary of some important studies into the safety and efficacy of MWA

Author	No. of patients	Type of study	CRLM specific (Y/N)	Morbidity (%)	Mortality (%)	Local recurrence (%)	Median follow-up (months)
Liu et al. [77]	35	Randomized	N	1.1	0	8.6	32.2
Correa-Gallego et al. [78]	67	Matched cohort	Y	27	0	6	18
Martin et al. [79]	20	Prospective	N	4	0	11.3	5
Iannitti et al. [80]	33	Prospective	Y	19	0	2.7	19
Zhou et al. [81]	35	Prospective	N	NR	NR	11.3	5

Cryoablation can be performed percutaneously with image guidance or laparoscopically. Cryoablative devices lower cell temperatures to cytotoxic levels through the formation of ice crystals. The ones used today employ the Joule-Thompson process to cool argon gas as it passes through a probe that is inserted into the target tissue [82]. During the freezing cycle, an "ice ball" that encompasses the tumor along with a 1 cm margin is formed, with multiple probes being used simultaneously for larger lesions [83, 84]. Like thermal ablation types, cryoablation is susceptible to a thermal sink effect; however in cryoablation, the risk stems from blood vessels bringing new, warm blood to the target tissue, hindering the effectiveness of the cooling.

The mechanism of cell death is multifaceted. The initial freezing event creates intracellular ice crystals, which disrupt the cell membrane [85]. These intracellular ice crystals also deplete the cells of water, causing multiple harmful effects. Additionally, the formation of ice in blood vessels can lead to ischemic injury [86].

The main advantage of cryoablation over other thermal ablative techniques is the clear visualization of the ice ball on ultrasound imaging or CT scan [82]. This allows for easy intraoperative monitoring of ablation margins.

While cryoablation is one of the oldest forms of ablation, the risk of complications is high compared to other techniques. Complications stemming from parenchyma shearing due to cracks forming in the ice ball include hemorrhage, biliary injury, and abscess formation [87]. Multiple studies have placed cryoablation-related complication rates between 20% and 30% for the treatment of CRLM [83, 88–90]. Additionally, a rare but serious risk of cryoablation is cryoshock syndrome [91]. Cryoshock is a cytokine-mediated systemic shock that, although rare overall, has been documented in multiple studies [84, 92, 93].

Comparisons between RFA and cryoablation have shown that recurrence rates tend to be higher in patients who underwent cryoablation versus those who underwent RFA for treatment of hepatic malignancies [83, 94]. See Table 36.4 for some of the important studies of cryoablation for hepatic tumors.

Table 36.4 Summary of some important studies into the safety and efficacy of cryoablation

Author	No. of patients	Type of study	CRLM specific (Y/N)	Morbidity (%)	Mortality (%)	Local recurrence (%)	Median follow-up (months)
Rivoire et al. [90]	24	Retrospective	Y	21	0	18	48
Yan et al. [88]	172	Prospective	Y	28	0	NR	23
Paganini et al. [89]	64 (49 open; 15 laparoscopic)	Retrospective	Y	26.2 (open); 6.7 (lap.)	4.1 (open); 0 (lap.)	0	39.3 (open); 87.1 (lap.)
Adam et al. [83]	31	Prospective	N	29	3.2	53	21.2
Bageacu et al. [84]	53	Retrospective	Y	66	3.8	22.6	24.8
Xu et al. [92]	326	Retrospective	Y	5.8	2.1	15.3	32
Pearson et al. [94]	54	Prospective	N	40.7	1.8	22.2	15
Kerkar et al. [93]	56	Retrospective	Y	11	11	NR	54

Nonthermal Techniques

Chemical Ablation

- Ethanol-ablation is simple and well tolerated.
- Presents high risk of local recurrence, requires multiple sessions, and ablation zone is variable.
- Limited value on CRLM due to its dense and infiltrative nature.

These techniques are useful to destroy tissues chemically with the use of either acetic acid or more commonly sterile ethanol. Percutaneous ethanol injection, also known as ethanol ablation, is a well-established and highly used ablation technique. Ethanol ablation involves the injection of ethanol directly into the target tissue. It requires no special equipment besides the injection needle and is usually conducted under the guidance of ultrasound [20, 85]. Small (20–22 gauge) needles are used to inject 95–100% ethanol [95]. The mechanism of cell death in ethanol ablation is dehydration of the cytoplasm, protein denaturation, and microvascular thrombosis [85, 96, 97].

The main benefit of ethanol ablation compared to the other modalities is its simplicity. Ethanol ablation is usually performed without general or local anesthetic and is well tolerated in the vast majority of patients. High local tumor progression rates and, although rare, hepatic necrosis are two main risk factors when considering ethanol ablation [98–100]. One relatively common side effect of ethanol ablation is nausea, and patients are instructed to fast prior to treatment [20].

Ethanol ablation safety has been well established for decades, but variable ablation zone size, the necessity of multiple sessions, and high local tumor progression rate compared to more modern techniques has led to it only being used in cases where tumor characteristics preclude the use of other modalities [85].

Irreversible Electrophoresis (IRE)

- IRE works with high-voltage pulses of electrical current to cause nanopore defects in the lipid bilayer of cell membranes.
- Requires general anesthesia combined with paralytic agents.
- It creates very sharp ablation margins and preservation of nearby vital structures.
- High major morbidity rate, safety, and efficacy still under study.

IRE is a newer form of surgical ablation. It was approved by the FDA for soft tissue ablation in 2006 [101]. The principle of IRE is to cause cell death through the application of electrical energy. IRE does not cause cell death through the same mechanism of any previously discussed techniques. Rather, IRE devices used today employ multiple electrodes inserted into the target tissue to apply short, high-voltage pulses of electrical current to cause nanopore defects in the lipid bilayer of cell membranes [85, 101]. The devices used typically deliver 90 pulses of 2–3 kV/cm for periods of a few milliseconds [85, 87]. Several studies have shown that the nanopores created led to cell death through both destabilization of the cell membrane and an increase in permeability [102–104].

Interestingly, the pores created by the electrical current application are extremely short-lived and often reversible if a certain threshold of electrical current is not met. Melikov et al. demonstrated that nanopores remained open for an average of just 3 +/− 0.8 ms at 250 mV [105]. The higher voltage used by IRE devices causes irreversible and persistent pores [85, 105].

IRE progress can be measured intraoperatively with ultrasound, but imaging changes to the ablation area can take several minutes to appear [106]. The technique also requires general anesthesia combined with paralytic agents to inhibit muscle activation by the electrical current [107].

There are several potential advantages IRE may hold. Because IRE utilizes effects of electrical current to directly damage cell membranes, it is not subject to the same heat-sink effect of the thermal modalities [87]. IRE has also been shown to create very sharp ablation margins and preservation of nearby vital structures, such as bile ducts and blood vessels, while showing successful ablation [108–111].

Hosein et al. conducted a retrospective analysis of IRE in CRLM in which 25 out of 29 patients had an absolute or relative contraindication to thermal ablation based on tumor size and location and found the procedure both safe and effective at destroying the tumor while preserving vital structures [112].

Complications of IRE were examined in a large systematic review conducted by Scheffer et al. in 2014. This review looked at the use of IRE in multiple organs, but found only minor complications reported for liver tumors treated with IRE [101]. However, some major complications associated with IRE have been reported. One study from 2016 of 65 malignant liver tumors in 34 patients reported major complications in 6 patients: 1 patient had diffuse intraperitoneal bleeding, 1 experienced partial thrombosis of the portal vein, and liver abscesses appeared in 4 patients [113].

Due to its recent surge in public interest, the literature on outcomes of IRE has mostly focused on assessing efficacy and safety. The review article published by Scheffer et al. mentioned previously concluded that IRE is safe and effective in otherwise untreatable liver tumors, but emphasizes that further study is needed to more thoroughly assess the possible role of IRE as a treatment option [101]. A more recent single-center study from 2017 reported that IRE was a safe treatment modality for liver tumors and achieved high local tumor control out to 6 months postoperatively [114].

Stereotactic Body Radiation Therapy (SBRT)

- SBRT implies delivery of high dosing, few fractions of radiation to a focal area of the liver.
- Well tolerated with minimal toxicity.
- Further studies needed to compare efficacy.

SBRT is also a relatively new form of surgical ablation. It allows delivery of higher doses in fewer fractions of radiation to discrete individual liver metastases, while sparing the normal hepatic tissue and surrounding organs [115]. The main challenge of SBRT to deliver radiation to the liver is managing respiratory movements. Various breathing control strategies such as respiratory gating and motion management techniques have been implemented to overcome this limitation, including the CyberKnife system (Accuracy Inc), which performs real-time tumor tracking. This allows for a high level of precision while treating the patient in free breathing and maintaining patient comfort [116].

Benefits from this technique include good local control of the disease with relatively low risks for major complications or toxicity. A recent retrospective study by Mahadevan et al. showed 427 patients with 568 liver metastases treated, with reasonable overall survival (median 22 months) and local control (median 52 months) on patients where most of the tumors were of colorectal origin [115]. Higher SBRT doses and smaller tumor volumes were associated with improved local control and overall survival. Because of the focal area of radiation delivered, toxicity from this

technique has been reported as minimal in the literature, but includes anorexia, fatigue, and some nausea, especially when left lobe of the liver is treated [117]. Due to the lack of randomized trials and comparative studies, further studies will be needed to compare the efficacies of SBRT with those of surgical resection or radiofrequency ablation.

Combining Surgical Resection with Ablative Techniques

As previously stated, the current standard of care involves surgical removal of CRLM as the only potential cure. However, whenever patients were not surgical candidates for curative resection due to major comorbidities, inadequate functional hepatic reserve, multifocal disease or a combination of these, most of the mentioned locoregional therapies are utilized as palliative treatment. Combining hepatectomy with ablative techniques allows the removal of the largest tumors while simultaneously ablating smaller residual tumors [118].

Recent studies have associated combined treatments including surgery and ablation, mostly using comparisons with RFA, but the information regarding outcomes may lack external validity since these are mostly limited to single-center studies. A meta-analysis published in 2015 on RFA versus liver resection on survival outcomes for CRLM concluded that liver resection was superior to RFA in survival outcomes and ablation should be reserved for patients who are not optimal candidates for resection until new supportive evidence is obtained from large randomized control trials [119].

More recently in 2016, Pawlik et al. conducted a study based on ACS-NSQIP database including patients undergoing liver resection and examined the patterns of these resections in North America, making emphasis on concurrent wedge resections and ablations [118]. The use of concurrent wedge surgical resection was observed in 56% of patients, more commonly among patients undergoing partial lobectomy compared to major hepatectomy. Concurrent ablations were performed in 14.2% of patients, also more often associated with partial resections. Prolonged length of stay, increased requirements of blood transfusions, and postoperative morbidity and mortality were more related to major hepatectomies than to ablative techniques. These results suggest that hepatectomy can be safely performed with concurrent ablation and could allow for more patients to undergo potentially curative therapy.

Conclusions and Recommendations

A large variety of ablative techniques are available to assist in the management of CRLM. Such techniques also expand the treatment options for disease recurrence in patients whose liver remnant is inadequate for surgical resection. General and liver-related comorbidities are common contraindications to hepatic resection and are often independent of the extent of disease or proposed operation. Many technical

factors make hepatic malignancies unresectable, including insufficient future liver remnant, involvement of all three hepatic veins, and involvement of portal inflow to both lobes of the liver. Many techniques to deal with technically unresectable tumors have been developed, such as portal vein embolization and two-stage operations. Nonetheless, most liver tumors are still unresectable. Currently, the most common ablative techniques include RFA and MWA. MWA has increased in utilization due to less heat-sink, the potential to address larger lesions, and lower operative time.

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