Review

Electrochemotherapy for Colorectal Liver Metastasis: What Interventional Radiologists Need to Know

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Abstract: The global burden of liver metastases from different primary lesions is increasing, resulting in significant challenges for public health systems. Accordingly, colorectal cancer (CRC) remains a leading cause of cancer-related mortality, with a high incidence of liver metastases. Although surgical resection is considered the standard curative treatment, it is only viable for a limited subset of patients. This review aims to describe a potential alternative nonsurgical intervention, such as electrochemotherapy (ECT), in the treatment of CRC oligometastatic liver disease. ECT has been largely used for the treatment of cutaneous and subcutaneous lesions, while its visceral use is currently a novel approach. ECT consists of the administration of intravenous anticancer drugs, followed by the application of intralesional electrode needles, which release localized electrical pulses to induce electroporation, a process that transiently increases cell membrane permeability, thereby facilitating the intracellular delivery of otherwise membrane-impermeable drugs. The main topics of this review focus on the technical and clinical applications, efficacy, safety, and possible complications of ECT for CRC liver metastases. A comparison with other locoregional treatments is also performed, highlighting possible advantages and disadvantages.

Keywords: electrochemotherapy; colorectal cancer; liver metastases; locoregional therapy

1. Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers globally, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths, with an estimated 1.9 million new cases and 935,000 deaths in 2020 alone [1]. The incidence of CRC varies significantly across regions, with the highest rates observed in high-income countries such as the United States, Canada, Australia, and much of Europe, where the disease primarily affects individuals aged 50 and older. However, there is a concerning trend of increasing CRC incidence among younger individuals, particularly in regions with Westernized lifestyles characterized by poor diet, physical inactivity, and obesity [2]. CRC is currently the third most frequently diagnosed cancer and the second leading cause of cancer-related deaths globally, with 25–30% of CRC patients progressing to develop liver metastases [2]. Liver metastases represent a significant challenge in oncology, often indicating an advanced-stage disease with a poor prognosis [3]. As the liver is a common site for metastatic spread from various primary cancers, including colorectal, breast,

and neuroendocrine tumors, effective local treatment options are crucial for improving patient outcomes [3]. Liver metastasis significantly impacts prognosis, with patients who have metastases typically experiencing a 5-year survival rate of less than 10%, compared to over 90% for those with localized disease [4]. While surgical resection remains the gold standard for curative intent, many patients are not suitable candidates due to the extent of disease, underlying liver dysfunction, or comorbidities [5]. In fact, only a quarter of CRC patients with liver metastases are eligible for resection [5]. Locoregional non-surgical interventions, including tumor ablation, offer alternative treatment strategies for patients who are not candidates for surgical resection. The European Society of Medical Oncology (ESMO) includes local ablation procedures in its consensus guidelines for metastatic colorectal cancer (mCRC) [6]. These interventions encompass thermal techniques such as radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, as well as non-thermal modalities like stereotactic body radiation therapy (SBRT), brachytherapy (also referred to as interventional radiotherapy, IRT), and both irreversible (IRE) and reversible electroporation, the latter which finds its application as electrochemotherapy (ECT) [7–13]. The selection of the best and most appropriate treatment is influenced by various factors, including the characteristics of the target lesion, and requires thorough discussion in multidisciplinary meetings in order to personalize the treatment for every patient and the lesion's characteristics [14]. Thermal ablation techniques are increasingly recognized as viable alternatives to open surgery for both primary and secondary liver tumors [15], although limitations exist regarding the size and number of target lesions according to the latest BCLC guidelines [16]. In such instances, chemoablation, particularly electrochemotherapy, represents a valuable adjunct to local treatment options. In recent years, ECT has emerged as a promising minimally invasive treatment modality for liver metastases. This technique combines the administration of chemotherapeutic agents with the application of electric pulses to the tumor site, enhancing drug uptake and cytotoxicity [17]. ECT has shown potential in treating various solid tumors, and its application in liver metastases has garnered increasing attention from clinicians and researchers alike [13]. The European Standard Operating Procedures for Electrochemotherapy (ESOPE) has established guidelines for the application of ECT in cutaneous tumors [18], and its efficacy has been extended to deep-seated tumors, including those in the liver. Being a non-thermal technique, ECT offers several advantages over other ablative treatments for the liver, such as its ability to treat lesions near or inside critical anatomical structures (i.e., main portal trunk, inferior vena cava, main biliary duct, hepatic artery) while sparing healthy tissues, the possibility of repetition, its independence from tumor histology, and its applicability as a local therapy between chemotherapy cycles of treatment. The existing literature indicates that patients generally tolerate ECT well, reporting minimal side effects and no significant discomfort, nausea, or systemic adverse effects [19,20]. The aim of this narrative review of the recent literature is to investigate the role of ECT in the treatment of mCRC, and to provide a comprehensive overview, covering its physical principles, procedural techniques, safety profile, adverse events, effectiveness, future perspectives, and ongoing clinical trials. By examining the current state of knowledge and ongoing research, we seek to elucidate the role of ECT in the management of liver metastases and its impact on patient care. Furthermore, a direct comparison with other locoregional treatments was made in order to facilitate the use of ECT in clinical practice, to underline the main advantages and disadvantages, and to help physicians in clinical applications.

Methodology

This review consisted of an advanced search on PubMed, Cochrane, and Scopus to identify comprehensive articles evaluating the efficacy and safety of electrochemotherapy in

mCRC with secondary liver lesions. The search focuses exclusively on full-text clinical studies of mCRC patients treated with ECT alone, excluding conference papers, surveys, letters, editorials, and book chapters. The search was also limited to English-language publications between 2003 and 2023, aimed to ensure relevance within the selected timeframe. The inclusion criteria encompassed randomized-controlled trials (RCTs), prospective, retrospective, and cohort studies utilizing percutaneous or surgical ECT.

2. Physical Principles

The fundamental principle underlying ECT is electroporation, a phenomenon in which the application of short, high-intensity electric pulses temporarily increases the permeability of cell membranes [19,20]. This process creates transient pores in the membrane's lipid bilayer, allowing for enhanced intracellular delivery of otherwise poorly permeable molecules, such as certain chemotherapeutic agents. Electroporation occurs when an external electric field of sufficient strength is applied to a cell, inducing a transmembrane voltage that exceeds a critical threshold. This leads to the formation of pores in the lipid bilayer, dramatically increasing membrane permeability. This process can be reversible or irreversible, depending on the electric field parameters and exposure duration. In the context of ECT, reversible electroporation is desired, as it allows for the temporary permeabilization of tumor cells without causing immediate cell death. This transient state enables the efficient uptake of chemotherapeutic agents, which can then exert their cytotoxic effects intracellularly [21,22]. The reversibility or irreversibility of electroporation mainly depends on two electric pulse characteristics: electric field strength and time pulse length. Many chemotherapeutics have been clinically tested in preclinical studies, but bleomycin and cisplatin are currently the two chemotherapeutics most used in association with ECT. After the drug administration, either intravenous or intratumoral, a short time interval is required for drugs to penetrate the tumoral tissue. Bleomycin is responsible for multiple DNA breaks, while cisplatin causes intrastrand and interstrand DNA bonds in tumoral tissue cells. ECT primarily utilizes the hydrophilic chemotherapeutic agents mentioned above, which normally have limited membrane permeability. The current most commonly used drug in clinical practice is bleomycin, a large, hydrophilic molecule with potent cytotoxic effects [23]. When combined with electroporation, the intracellular concentration of bleomycin can increase by several orders of magnitude, significantly enhancing its therapeutic efficacy. The cytotoxic effect of antitumoral drugs in ECT is increased 1000-fold for bleomycin and 80-fold for cisplatin; cells in the active mitotic phase may exhibit non-repairable DNA damage due to the action of bleomycin or cisplatin and induce cell apoptosis [24]. In addition to enhancing drug delivery, the application of electric pulses in ECT has been observed to induce a transient "vascular lock" in the treated area. This phenomenon, characterized by a reduction in blood flow, can contribute to the treatment's effectiveness by prolonging the exposure of tumor cells to the chemotherapeutic agent and potentially inducing ischemic damage to the tumor tissue [25]. Emerging evidence suggests that ECT may have a role in the immune response. The localized cell death induced by ECT can lead to the release of tumor antigens and damage-associated molecular patterns (DAMPs), potentially activating the immune system against the tumor. Since ECT does not cause protein denaturation, any tumor-specific antigen may be released in its intact form and recognized by inflammatory cells that migrate to the tumor lesion [26,27].

3. Procedural Technique

Electrochemotherapy on liver metastases can be performed percutaneously, laparoscopically, or during open surgery, depending on the tumor location, size, and number of lesions [28,29]. Prior to the procedure, detailed imaging studies, typically contrast-

enhanced CT or MRI, are performed to accurately locate and characterize the liver metastases (Figure 1). This information is crucial for treatment planning, including electrode placement and determination of the treatment volume. The chemotherapeutic agent, most commonly bleomycin, is administered either intravenously or intratumorally. For intravenous administration, bleomycin is typically given at a dose of 15,000 IU/m^2 body surface area. The electric pulses are applied within a specific time window after drug administration, usually 8–28 min for intravenous bleomycin, to ensure optimal intratumoral drug concentration. Electrode placement into the lesion is a critical step in the ECT procedure, and its planning must be carefully performed in order to achieve the best clinical results. Various electrode configurations are available, including needle electrodes for deep-seated tumors and plate electrodes for superficial lesions [30]. For liver metastases, multiple long single-needle electrodes or hexagonal electrode arrays are often used [30,31]. The electrodes are inserted into and around the neoplasm under imaging guidance, typically ultrasound or CT, to ensure accurate positioning (Figure 2) [32]. The arrangement of electrodes aims to create an electric field that encompasses the entire tumor volume and a safety margin of surrounding tissue [33]. Once the electrodes are in place and the optimal time window for drug distribution is reached, electric pulses are delivered using the electroporation device. The standard ECT protocol typically involves the application of eight pulses of 100 μs duration at a frequency ranging from 1 Hz to 5 kHz, with a median duration of 25 min. The applied voltage is adjusted based on the distance between electrodes to achieve the desired electric field strength, usually around 1000 V/cm. For patients with multiple liver metastases, the procedure can be repeated to treat different lesions in the same session. However, care must be taken to avoid exceeding the maximum safe dose of the chemotherapeutic agent, which is capped at 30,000 IU/m^2, adjusted by age and creatinine [34]. Following the procedure, patients are monitored for potential complications and treatment response. Imaging studies are typically performed at regular intervals to assess tumor response and to guide further management.
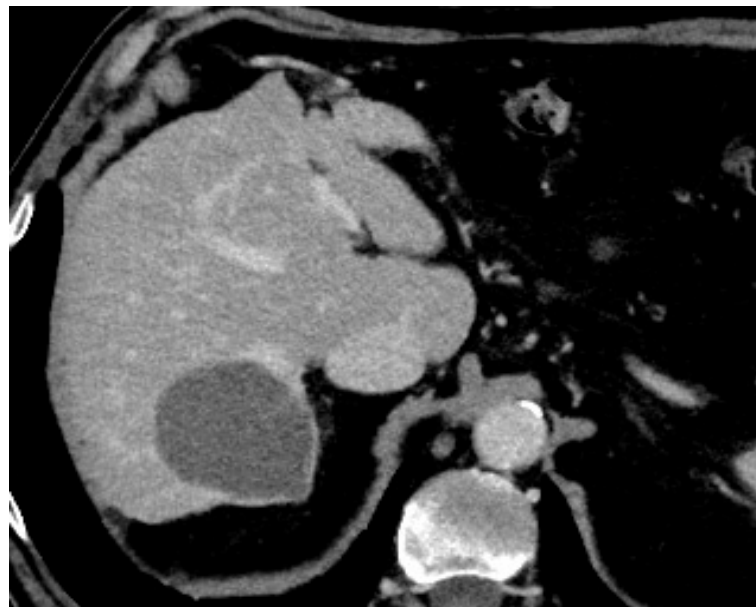

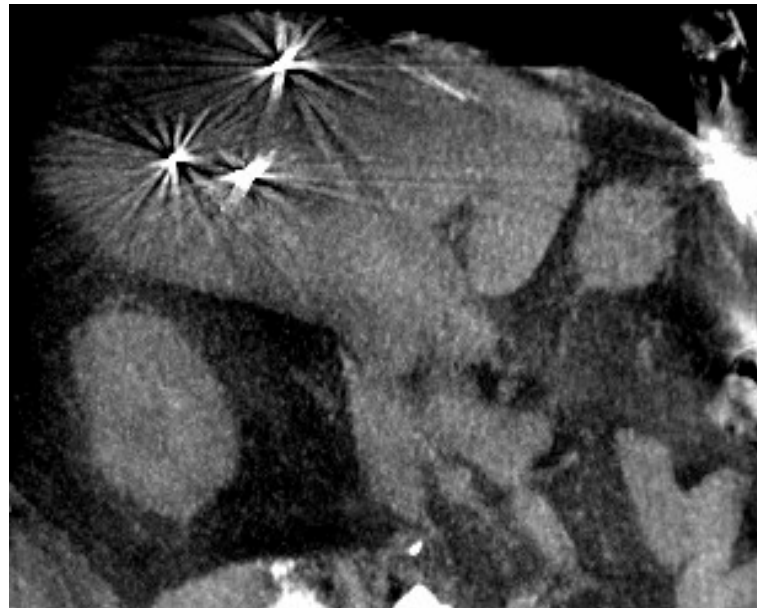**Figure 1.** Metastases of CRC, hepatic dome.

Figure 2. ECT, electrode insertion encompassing lesion.

4. Safety

ECT for liver metastases has demonstrated a favorable safety profile in clinical studies, with a low rate of serious adverse events [35]. However, as with any medical procedure, there are potential risks and safety considerations that need to be addressed. Proper patient selection is crucial for ensuring the safety and efficacy of ECT. Patient stratification plays a critical role in clinical outcomes, with particular attention to liver function and performance status. Contraindications to ECT include severe coagulation disorders, significant cardiac arrhythmias, and epilepsy. Furthermore, several safety measures are necessary during the ECT procedure, including cardiac synchronization with the electrocardiogram (ECG), to avoid the vulnerable period of the cardiac cycle during electric pulse delivery, reducing the risk of arrhythmias [36]. It is important to perform ECT under general anesthesia or deep sedation, with careful and constant monitoring of vital signs, in a fully equipped suite. A two-step analgosedation has been described, proposing an initial collaboration of the patient during needle insertion using superficial sedation only, via administration of midazolam (0.01–0.02 mg/kg), followed by a deep sedation with propofol and remifentanil [37]. From a technical point of view, when treating liver lesions, special attention must be paid to protecting surrounding structures, to avoid non-target positioning of the needle electrodes and subsequent organ perforation. Nonetheless, several studies have demonstrated a good safety profile of ECT, with neither indirect nor heat-/electric-induced effects on surrounding structures during the activation of the needles, nor thrombosis or other clinically significant damage to large blood vessels and bile ducts in the liver [38,39].

5. Adverse Events

Even though ECT is generally well tolerated by patients, various adverse events have been reported in clinical studies. Adverse events associated with ECT for liver metastases are mostly transient, mild to moderate in severity, mainly related to drug-induced alterations, and can be managed conservatively. Post-procedural pain is common but usually manageable with off-the-counter analgesics. Fever, nausea, vomiting, and diarrhea are often related to the chemotherapeutic agent and can be controlled with medical therapy. Patients may experience fatigue for several days following the procedure. Bleomycin can determine dermatographism as well as skin hyperpigmentation in body parts that

undergo traumatism during the treatment (e.g., adhesive tape for intubation, ECG electrode placement) [40]. A mild to moderate increase in liver enzymes is common and usually resolves spontaneously. Systemic administration of bleomycin can cause myalgia, which is usually self-limiting. While rare, bleomycin-induced lung fibrosis is a potential concern, particularly in patients with pre-existing lung disease or those receiving high cumulative doses; a pre-treatment chest CT evaluation is therefore useful for patient screening. Proper patient education, close monitoring, and prompt intervention when necessary are key to minimizing the impact of these events on patient outcomes.

6. Effectiveness

The effectiveness of ECT for liver metastases has been demonstrated in several clinical studies [28,35,41,42], although large-scale and multi-centric randomized controlled trials are still lacking. The assessment of treatment efficacy typically involves the evaluation of tumor response, local control rates, and the impact on patient survival. Tumor response to ECT is generally assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) or modified RECIST (mRECIST) criteria. In a study by Spallek and colleagues, the objective response rate (ORR) was 85.7% (complete response (CR) 61.9%, partial response (PR) 23.8%); the mean progression-free survival (PFS) was 9.0 ± 8.2 months, and the overall survival (OS) was 11.3 ± 8.6 months [41]. ECT showed the best performance (in terms of PFS and OS) in lesions between 3 and 6 cm in diameter ($p = 0.0242$ and $p = 0.0297$, respectively). The efficacy of ECT did not depend on the localization of the lesion. PFS and OS were independent of the histology of the treated lesion [41]. In a study by Edhemovic and colleagues, the tumor response rate (ORR) was 75%, with 63% of patients achieving CR and 12% achieving PR. The median response duration was 20.8 months for metastases classified as CR, and 9.8 months for those classified as PR. The treatment exhibited significantly greater efficacy for metastases measuring less than 3 cm in diameter compared to larger lesions. No differences in response rates were observed based on the location of the metastases, whether central or peripheral. Furthermore, PFS was more favorable in patients who exhibited a CR to ECT compared to those with a PR or progressive disease (PD). However, OS did not differ significantly, with a median of 29.0 months [28]. Coletti and colleagues performed ECT on a total of nine CRC liver metastases, which were treated across five patients using 20 electrode applications. No intraoperative complications were recorded. At 30 days post-treatment, the CR rate was 55.5%, while stable disease (SD) was observed in 45.5% of cases. All five patients achieved an OS of 6 months, and four out of the five patients experienced PFS for 6 months [29].

7. Comparison with Other Methods

While direct comparative studies are limited, ECT has shown promising results when compared to other local therapies for liver metastases, offering several unique advantages: in particular, its capacity to spare normal liver parenchyma, and to avoid thermal injuries and surgery-related complications.

7.1. Systemic Chemotherapy

Systemic chemotherapy remains the backbone of treatment for many mCRC patients, especially those with extrahepatic spread. In the case of metastatic liver cancer, adjuvant systemic chemotherapy can be added to ECT for better tumor burden control at the discretion of the referring oncologist [29]. However, systemic side effects can be significant, and chemotherapeutic drugs may show limitations against some tumor types, with the development of drug resistance over time [14].

7.2. Surgical Resection

Surgical resection is still considered the gold standard for curative-intent treatment of oligometastatic liver disease when feasible, with the possibility to provide tissue for pathological assessment [43]. The main disadvantages of surgery are related to its invasiveness and associated surgical risks, as well as limitations to patients with adequate liver function, and to anatomical resectability of the disease [14]. Moreover, patients with comorbidities cannot undergo major surgery or general anesthesia, and some patients eventually refuse surgical intervention. In addition, it is often difficult to achieve a complete surgical curative endpoint (R0) with metastasectomy, due to an extensive burden of disease. In this case, a hepatectomy should be taken into consideration, and future liver remnant volume evaluation represents one of the main concerns to avoid post-surgical liver failure [44]. In the case of inadequate future liver remnant volume, hepatectomy must be preceded by a right portal ligation or embolization, which might be combined with hepatic vein ligation or occlusion to maximize the future liver remnant volume increase in size [45]. In case of patients unfit for surgical resection due to lesion location, comorbidities, or patient refusal, ECT can represent a viable alternative.

7.3. Thermal Ablation

When compared to thermal ablative techniques such as RFA or MWA for liver metastases, ECT has the main advantage of treating lesions with anatomical difficulties; thanks to its non-thermal mechanism, a "gating" is performed around the lesion. Needle electrodes may be placed even outside the liver, adjacent to subcapsular lesions, due to the thin size of the employed needles (up to 21-G) [42,46]. The main advantages of ECT, thus, consist of treating lesions near large vessels (as it does not lead to vessel damage, and is unhindered by the heat-sink effect), near central biliary structures (e.g., right or left biliary ducts, main biliary duct), and near critical extra-hepatic structures such as the diaphragm, colon, or stomach [47]. The versatility of the ECT in needle electrode placing and intra-procedural electrode swapping permits the treatment of larger lesions compared to RFA and MWA, according to clinical indications, either in downstaging of the disease, tumor burden and local control, or in curative planning [48].

7.4. Transarterial Chemoembolization (TACE)

TACE involves the injection of chemotherapeutic drugs combined with embolic agents into the hepatic artery supplying the tumor. In particular, drug-eluting beads plus irinotecan (DEBIRI) TACE is the main option for intra-arterial treatment of CRC liver metastatic lesions [49]. A 2 mL suspension of microparticles with a diameter of ≤ 100 μm, containing irinotecan at a concentration of 50 mg/mL (totaling 100 mg per syringe), is slowly infused, usually alongside 5 mL of sterile water for injection and 10 mL of non-ionic contrast medium. The infusion continues until the complete intended dose is administered. The procedural objective is to achieve the targeted dose of the anticancer agent while maintaining vessel patency, aiming for a state of "near-stasis" flow, while still maintaining a combined ischemic effect. The main advantage of TACE in comparison to ECT is the treatment of extensive hepatic burden in one or more sessions, especially when bilobar involvement is assessed. However, as an intra-arterial procedure, its main disadvantages consist of the risks of post-embolization syndrome and non-target embolization. Moreover, as DEBIRI-TACE is focused on tumor burden control, it is considered mostly as a palliative therapy in patients non-responding to chemotherapy rather than a curative treatment [50].

7.5. Transarterial Radioembolization (TARE)

TARE might be a valuable option in the treatment of liver metastases by intra-arterial administration of resin or glass microspheres loaded with Yttrium-90 (Y90) or other isotopes [51]. The main advantage of TARE is the ability to treat diffuse intralobar disease while simultaneously determining contralateral liver hypertrophy, which can be useful in cases of planned hepatectomy (bridge to surgery) due to the actinic effect of microspheres [52]. Moreover, since portal thrombosis remains a relative contraindication for the procedure, it might be used in this specific situation. Similarly, ECT is suitable for treating lesions with associated portal thrombosis and also for treating neoplastic portal invasive lesions [42]. The main disadvantages of TARE consist of possible non-target delivery of the microspheres, leading to radiation-induced gastritis and gastric ulcers, pancreatitis, and cholecystitis [52]. ECT may offer an advantage over TARE in terms of repeatability and lack of radiation exposure.

8. Combination Strategies

There is growing interest in combining ECT with other treatment modalities to enhance therapeutic efficacy; the potential synergy between ECT and immunotherapy agents, such as checkpoint inhibitors, is an area of active research [53]. Currently, this combination is employed in the treatment of cutaneous and subcutaneous primary and metastatic lesions, but in the future, it might be extended to visceral applications [54]. Furthermore, recent findings suggest that electrochemotherapy (ECT), in conjunction with immunotherapy, may result in a better systemic response to tumors [54]. Calcium electroporation is a novel type of electrotherapy-based treatment, currently under investigation, which involves high-voltage pulses to permeabilize cell membranes and permits a high dose of calcium to enter the cell. The cell usually maintains an adequate level of calcium at micromolar doses by its exchange with a calcium ATPase. High levels of intracellular Ca++ lead to cellular apoptosis [55,56]. Currently, calcium electroporation is tested on cutaneous lesions, but in the near future, it might also be tested on visceral lesions [57]. Gene electrotransfer (GET) is a promising non-viral gene delivery method that uses electric pulses to temporarily increase cell membrane permeability, facilitating DNA uptake [58]. It offers advantages in safety, flexibility, and cost, with applications ranging from cancer treatment to DNA vaccination. Understanding the underlying mechanisms and scaling up to human applications is currently under in vitro and in vivo investigation. Despite these hurdles, GET has shown potential in enhancing immune responses in DNA vaccination and delivering therapeutic genes for cancer treatment, with ongoing clinical trials demonstrating its safety and efficacy.

9. Future Perspectives and Ongoing Trials

Currently, a European-wide, prospective, observational cohort registry (REgiStry for Percutaneous ElectroChemoTherapy—RESPECT) is enrolling and collecting data from patients with primary or secondary liver cancer treated with percutaneous ECT. The main endpoint of the study is to assess the effectiveness of ECT in controlling primary and secondary liver cancer, evaluating the 12-month local tumor control, whereas secondary endpoints are the assessment of patient safety, OS and PFS, patient's quality of life, and pain [59].

10. Conclusions

In conclusion, ECT represents a promising minimally invasive treatment option for liver metastases. Its unique mechanism of action, favorable safety profile, and encouraging efficacy results make it an attractive alternative or complement to existing therapies. The safety profile and manageable adverse event spectrum of ECT make it an attractive option

for patients with liver metastases, particularly those who may not be candidates for more invasive treatments. As ongoing research continues to optimize treatment protocols and explore novel applications, ECT is poised to play an increasingly important role in the multidisciplinary management of patients with liver metastases. Understanding its physical principles is crucial for optimizing ECT protocols and expanding its applications in the treatment of liver metastases. As research in this field progresses, refinements in our understanding of these mechanisms will likely lead to improved treatment outcomes and broader clinical adoption. The decision to treat liver metastases with ECT depends on various factors, including tumor characteristics, patient condition, device availability, and operator expertise. This should be considered in the context of a multidisciplinary tumor board discussion to tailor the most appropriate treatment for the patient's needs, whether alone or in combination with other treatment modalities. Moreover, ongoing vigilance and reporting of adverse events are crucial for continually refining the safety protocols and improving patient care.

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