Local Ablation for Solid Tumor Liver Metastases: Techniques and Treatment Efficacy

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Background: Treatment options for liver metastases from solid tumors, such as colon cancer, breast cancer, neuroendocrine tumors, and sarcomas, have expanded in recent years and now include nonresection methods. Methods: The literature focused on the treatment of liver metastases was reviewed for technique, perioperative, and long-term outcomes specifically related to local ablation techniques for liver metastases. Results: Ablation modalities have become popular as therapies for patients who are not appropriate candidates for surgical resection. Use of these techniques, alone or in combination with other liver-directed therapies (and often systemic therapy), has extended the rate of survival for patients with liver metastases and, at times, offers nearly equivalent disease-free survival rates to surgical resection. Conclusions: Although surgical resection remains the optimal treatment for liver metastasis, local options, including microwave ablation and radiofrequency ablation, can offer similar long-term local control in appropriately selected patients.

Introduction
Liver metastases occur as the sole site of metastatic disease in many solid neoplasms, commonly from colorectal adenocarcinoma or breast carcinoma. However, other malignancies, such as pancreatic adenocarcinoma, neuroendocrine tumors, and gastrointestinal stromal tumors, can also present with liver metastases as the site of metastatic disease. The options for liver-directed therapies have expanded in the last several decades and now include intra-arterial chemotherapy, radiation, and local ablative techniques. Although this review will not address intra-arterial embolization or perfusion options, multiple techniques are often utilized in a complementary manner to treat disease.

Surgical resection, sometimes in a staged-fashion or as repeat resections, for liver-only metastatic disease has remained the gold standard of treatment, providing the best rates of disease-free survival (DFS) and overall survival (OS). However, patient or tumor factors may preclude surgical resection. Liver-directed ablation has also emerged as an important and often effective alternative to surgical resection for these patients, frequently providing a survival benefit over chemotherapy or palliative care alone.

Liver ablation was first described in the 1980s with the use of ethanol injections for primary and secondary hepatic tumors; around this time, use of cryotherapy was also described, and high-intensity ultrasonography was being investigated as a way of creating necrosis within hepatic tumors in animal studies. The past several decades have provided us...
with a deeper understanding of the technology, the clinical impact of treatment for hepatic tumors from metastatic disease, and the development of newer and safer techniques.

Cryotherapy
Cryotherapy was initially reported in the late 1970s and involved using ultrasonography to guide the placement of a cryoprobe into the center of a lesion. The tip of the cryoprobe contains liquid nitrogen circulating at -196 °C, and freezing is continued until a 1-cm diameter of hypoechogenicity is circumferentially achieved, thus creating an “iceball.” A thaw cycle then commences by circulating nitrogen at room temperature, at which point the probe can be removed or additional freeze cycles can be performed. Adverse events from cryoablation include hepatic bleeding from parenchymal cracks, which can be potentiated by thrombocytopenia and coagulopathy seen in hepatic cryosurgery; in addition, operative times are typically long because of the technique utilized to create an “iceball.” However, the modality has fallen out of favor and has been largely replaced with thermal ablation techniques.

Thermal Ablation
Similar to cryotherapy, radiofrequency ablation (RFA) uses ultrasonographic guidance to place a probe into the center of the lesion; the procedure can then be performed in a monopolar or bipolar manner. High-frequency alternating currents from the electrodes cause heat to form due to ionic agitation, thus resulting in thermal ablation. Heating around the tip of the electrode can be intensified by increasing the power of the generator, thus inducing a significant volume of necrosis and char formation, thereby limiting further current flow. Sustained temperatures higher than 50 °C result in coagulation necrosis, and overlapping ablations are often used to ensure that the tumor area has been adequately covered. In general, contraindications to the procedure include proximity of the tumor to the bile duct or major intrahepatic vessels, coagulopathy, or tumor size above 5 cm. A limitation to use of RFA is the “heat sink” effect, which is related to the decrease in temperature from ablation in proximity to blood vessels, which is particularly true for large vessels with faster blood flow. Data have shown that the maximal temperature can be decreased by up to 21% when ablating in proximity to large vessels, and this phenomenon is thought to limit the efficacy of RFA around vessels.

Microwave ablation is a modality that also achieves tumor necrosis through heat, which is produced by the conduction of microwave energy. Tissues with a higher concentration of water, such as liver, are most conducive to this type of heat because the microwave energy causes the water molecules to realign. Microwave energy can also conduct through charred or desiccated tissue, unlike RFA, and can achieve higher temperatures than RFA (up to 180 °C). Microwave ablation also seems less affected by thermal convection from adjacent vessels.

Postablation Syndrome
A self-limited, flulike constellation of symptoms, including fever, pain, nausea, vomiting, malaise, and myalgia, has been described following both RFA and microwave ablation and is commonly referred to as postablation syndrome. Prospective survey studies have reported incidences of these symptoms ranging from 32% to 81% in some patients. Onset of these symptoms typically occurs within 24 to 48 hours following the procedure, and symptom resolution is typically within 10 days, although some symptoms may persist for up to 3 weeks. In most patients, these symptoms can be managed with nonsteroidal anti-inflammatory drugs. Factors predictive of the syndrome may include tumor volume (> 4.5 cm), ablation volume, length of ablation (> 20 minutes), and significantly elevated postablation levels of aspartate transaminase.

Complications
Most complications associated with use of RFA and microwave ablation are consequences relating to thermal injury. The risk of periprocedural mortality following ablation in the absence of combined hepatic resection is low and ranges from 0.1% to 0.5%. Major complication rates range from 2.8% to 9.5%, and these types of complications are more commonly seen with open ablation and in patients with underlying cirrhosis. The most commonly reported early complications include symptomatic pleural effusion, hemorrhage, perihepatic/hepatic abscess, biloma, liver dysfunction (occurring almost exclusively in patients with cirrhosis), portal venous thrombosis, and hemothorax/pneumothorax. Thermal injury to adjacent structures, most commonly the stomach, has also been reported, but this complication is rare and can be generally avoided with careful patient selection and meticulous technique. Late procedure–associated complications are rare (≤ 2.4%) but can be significant. Such complications include liver abscess, biloma, biliary fistula, bile duct stricture, arteriovenous fistula, hepatic abscess, diaphragmatic hernia, gastric perforation, and intractable pain.

Irreversible Electroporation
Irreversible electroporation (IRE) represents a recent modality that has been used for liver ablation. Electroporation involves applying high-voltage electricity that is delivered in short pulses across a cell membrane, resulting in changes in the electrochemical...
potential of the cell membrane and subsequent instability. This instability causes pores to form in the membrane, an effect that allows the introduction of macromolecules, drugs, and, in some cases, genes into the cell.26 Prolonged application of the electric stimulation will result in irreversible porosity (ie, IRE) of the cell membrane, ultimately leading to cell death.26 The preservation of the structural integrity of nearby vital structures has also been reported, thus making IRE an ideal option for lesions located adjacent to vascular or biliary structures.27,28

Because IRE is a relatively new technique, its associated complications and their incidence are not well described; however, several complications have been observed and are important to mention. Because IRE relies on high-voltage electrical pulses, cardiac arrhythmias and severe muscle contractions may occur.27,29,30 Complete neuromuscular blockade during the procedure prevents muscle contraction and patient movement.27,28 As experience with the technique has accumulated, modifications to the technique (eg, synchronization with electrocardiography so that the electrical pulses are administered during the absolute myocardial refractory period) have been developed to prevent life-threatening arrhythmias, such as ventricular fibrillation, from occurring.27 However, technique modification has not eliminated the incidence of transient atrial arrhythmias, which still occur in approximately 2% of patients.27,30 During the procedure, increases in both systolic and diastolic blood pressure may be seen; in addition, increases in transaminase and lactate levels following the procedure are frequently observed, although these increases typically resolve within 3 days.29,31

Although existing data on IRE are still relatively new, 1 systematic review found no periprocedural mortalities and a 16% overall complication rate, with no complications deemed to be major.50 The cohort of study patients analyzed included a large proportion of treated tumors located near major vascular or biliary structures, and a 6% rate of thrombosis or stricture of these structures was observed.50 The study authors hypothesized that this may have been due to the development of heat adjacent to the electrodes, so they recommended against placing electrodes within 2 mm of central bile ducts or the intestines to avoid such complications.50 Other adverse events of IRE include dehydration, biliary stent occlusion, acute renal failure, neurogenic bladder, and abdominal/flank pain.27

Procedural Approach
Although overall familiarity with these techniques has been expanding during the past 10 years, reliable interpretation of ultrasonographic imaging and the accurate placement of probes remain limitations of the technology. In addition, although effective ablation can be reliably achieved in small (< 3 cm) tumors, ablation of larger tumors may be compromised by accurate targeting, the proximity of these tumors to vascular or biliary structures, or risk of postablation complications. Use of ablation via laparotomy may appear to result in few local recurrences, but no randomized trial has been performed to date that has compared approaches for ablation delivery; moreover, multiple factors (eg, lesion number, size, location) influence recurrence.52

Percutaneous approaches are the least invasive and may be better suited for patients with small lesions deep in the hepatic parenchyma or those patients who are not candidates for surgical resection or surgical ablation.53 Instilling intraperitoneal fluid to create artificial ascites has been suggested as a means to protect adjacent structures and potentially allow for more aggressive patient selection for percutaneous ablation.54 A surgical approach, using either an open or laparoscopic technique, is better suited for patients with peripheral lesions or lesions located near the hepatic or portal veins; in the latter group, hepatic vascular inflow occlusion, via a Pringle maneuver, may help the clinician achieve adequate ablation temperatures.55

Surgery vs Chemotherapy
Thus far, no randomized controlled trial has compared RFA with surgical resection for colorectal or other liver metastases, and only a single, phase 2 randomized controlled trial has compared systemic therapy with systemic therapy in combination with RFA for unresectable colorectal liver metastases.56 Ruers et al56 compared systemic therapy with or without RFA, but their study was slow to accrue and was closed early. Although the study met its primary end point of a 30-month OS rate of greater than 53% in the combined treatment arm, the OS rate for those assigned to the chemotherapy-alone arm was higher than anticipated, and the difference in rate of survival between the 2 arms was not significantly different at a median follow-up period of 4.4 years.56 However, the median progression-free survival rate (PFS) was 16.8 months in the combined treatment group compared with 9.9 months in the chemotherapy-alone arm, a difference that was statistically significant (95% confidence interval [CI], 9.3–13.7).55 Long-term follow-up data from this study have not yet been published, so whether a difference in OS will emerge remains to be seen. Data from prospective studies comparing microwave ablation or IRE with chemotherapy have not yet been published.

In 2008, Mulier et al36 published data from a phase 3, prospective, randomized controlled trial begun in 2002 comparing liver resection and RFA for small colorectal metastases, but the study failed due to lack of accrual. Although no prospective, randomized controlled trial has compared RFA and surgical resection for colorectal metastases, the best available data
consist of a meta-analysis, a Markov decision analysis, and a retrospective comparison of data from 2 prospective trials.57-40

One meta-analysis included 13 studies — all but 1 was a retrospective study — and found that liver resection resulted in superior rates of OS (relative ratio [RR] 5-year OS, 1.47; 95% CI, 1.28—1.69) and DFS (RR 5-year DFS, 2.23; 95% CI, 1.82—2.72) compared with those seen with RFA.57 Those results held up in a subset analysis limited to study patients with solitary tumors of less than 3 cm in size.57

A Markov decision analysis compared hepatic resection with percutaneous or laparoscopic RFA and predicted a mean quality-adjusted life expectancy rate of 5.67 ± 0.71 years with a 5-year survival rate of 38.2% following liver resection compared with a mean quality-adjusted life expectancy rate of 3.61 ± 0.49 years with a 5-year survival rate of 27.2% for RFA.38 However, this study also reported on a single-institution, prospective database of patients treated with laparoscopic RFA for resectable tumors, and it predicted a mean quality-adjusted life expectancy rate of 5.72 ± 0.5 years for RFA — a rate that exceeded liver resection.58

Tanis et al39 compared the results of local control among study participants assigned to RFA with study patients assigned to resection who had colorectal metastases and tumors at least 4 cm in size and were given perioperative folinic acid/fluorouracil/oxaliplatin. When the analysis of results after RFA was limited to tumors of no more than 3 cm in size, the local recurrence rate (median follow-up time, 4.7 years) was 2.9% per lesion, which compared favorably with the local recurrence rate of 6.0% per lesion in the resection cohort.59

A single, small, prospective, randomized trial compared the use of microwave ablation and resection for resectable colorectal liver metastases.40 The researchers reported equivalent 1-, 2-, and 3-year survival rates between the 2 therapies, as well as significantly less intraoperative blood loss with microwave ablation.40

Based on these results, RFA and microwave ablation are reasonable alternatives to liver resection in patients with small colorectal metastases, and this is particularly true in patients for whom liver resection would carry a higher-than-average risk of morbidity or mortality.

Colorectal Metastases

Radiofrequency Ablation

Prospective data on the long-term outcomes after RFA for colorectal liver metastases are limited.35,57,41 A study conducted by Evrard et al41 was a multicenter, single arm, nonrandomized phase 2 trial that evaluated the effectiveness of RFA with or without resection for the treatment of unresectable metastases. After a median follow-up time of 2.9 years, the researchers observed a 3-year event-free survival rate of 10% and a 5-year OS rate of 43%.41 Ruers et al35 headed a phase 2 trial and reported a median OS rate of 45.3 months for study patients with unresectable colorectal liver metastases who were treated with RFA and chemotherapy. Retrospective studies have reported 3-year OS rates ranging from 32% to 84% and 5-year OS rates ranging from 17.9% to 49%, with 3-year DFS rates ranging from 0% to 76% and 5-year DFS rates ranging from 0% to 69.7%.37

A report from Gillams et al42 advocated use of thermal ablation for unresectable lesions, predominantly in the form of RFA, for colorectal liver metastases, noting that the best outcomes occur in tumors smaller than 3 cm in size, located more than 1 cm away from bile ducts or major blood vessels, and have an ablation margin greater than 1 cm.

Microwave Ablation

A randomized trial comparing microwave ablation and liver resection for the treatment of resectable colorectal liver metastases found that study patients treated with microwave ablation had 1-, 2-, and 3-year OS rates of 71%, 57%, and 14%, respectively, and a mean survival time of 27 months; thus, the survival rates were comparable with the resection group.40

A retrospective study evaluating the long-term outcomes following microwave ablation included patients treated with microwave ablation alone and in combination with resection — 48.3% of whom were also treated with hepatic arterial infusion chemotherapy.43 This study reported a 4-year OS rate of 58.3% for those participants with colorectal liver metastases.43 The researchers also noted that local recurrence rates were higher for lesions larger than 3 cm in diameter and in those located in close proximity to major vessels or in a subcapsular location.43

An early experience with ultrasonographic-guided microwave ablation reported a clinical success ablation rate of 100%; however, local tumor progression was seen in 9.6% of treated metastases.44

Irreversible Electroporation

Long-term outcome data after IRE for colorectal liver metastases are lacking. A prospective registry study reporting on IRE for tumors located adjacent to major biliary and vascular structures found a 12-month local recurrence-free survival rate of 59.5%.27 One retrospective study of IRE for colorectal metastases described a 2-year OS rate of 62%.45

Noncolorectal Metastases

RFA has also been used for the treatment of noncolorectal liver metastases, particularly those without a dominant blood supply from the hepatic artery; those predominantly supplied by the hepatic artery are preferentially treated with chemoembolization. Taşçi et al46
conducted a retrospective study of patients with liver metastases from breast cancer treated with laparoscopic RFA and reported a median OS rate of 47 months and a 5-year survival rate of 29% following a diagnosis of liver metastases. Pawlik et al reported on outcomes after RFA with or without resection for sarcoma liver metastases and observed 1-, 3-, and 5-year OS rates of 91.2%, 65.4%, and 27.1%, respectively. A prospective study of arterial infusion chemotherapy followed by RFA for liver metastases from gastric adenocarcinoma observed a median survival rate of 16.5 months.

Given these study data, there is a potential role and survival benefit for hepatic ablation in carefully selected patients with noncolorectal liver metastases.

Conclusions

The technology and techniques used for ablation to treat liver metastases have continued to evolve in the past several decades and now include thermal methods, such as radiofrequency ablation and microwave ablation, as well as nonthermal methods such as irreversible electroporation. Although it is commonly performed in conjunction with systemic therapy or other liver-directed treatment, ablation may offer a survival benefit for patients with metastatic disease in the liver. This is particularly true for small lesions not located adjacent to biliary or vascular structures.

Further development of techniques to enhance ablation and study ablative methods as part of multimodality treatment may help patients achieve survival rates that approach those of surgical resection, the current treatment of choice.

References


