Combining Locoregional Therapies in the Treatment of Hepatocellular Carcinoma

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Abstract

In an effort to promote more durable local control of larger lesions, thermal ablation has been combined with chemical ablative techniques and with vaso-occlusive procedures such as chemoembolization and bland embolization in an effort to mitigate the limitations inherent in the use of any single treatment for hepatocellular carcinoma (HCC) >3 cm. The heat-sink effect is the underlying principle for combining vaso-occlusive therapies with ablative techniques. Combination therapies do present viable options for abrogating tumor progression and potentially downsizing tumors to facilitate transplant. We discuss the two most commonly used combination locoregional therapies by the interventionalist and the evidence defining the best techniques in practice.

Keywords

- interventional radiology
- hepatoma
- ablation
- chemoembolization
- combination therapy

Objectives: Upon completion of this article, the reader will be able to identify the role of combination therapy, including technical aspects and clinical outcomes, in the treatment of primary and secondary tumors of the liver.

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Surgical resection is the first-line therapy for patients with hepatocellular carcinoma (HCC) with intermediate- or large-size tumors. However, due to compromised hepatic reserve secondary to underlying chronic liver disease, only 5 to 40% of patients are ultimately candidates for hepatectomy.[1] Locoregional therapies, including chemical or thermal ablation and transarterial embolization, have emerged as the primary therapies for unresectable HCC. Modalities for ablation include radiofrequency ablation (RFA), microwave, laser, ethanol, and cryoablation. Local ablative techniques are effective for small HCC, with complete necrosis of 76 to 100% for tumors <3 cm after a single ablation session.[2–4] More challenging to treat are intermediate (3.1 to 5.0 cm) and large (>5 cm diameter) lesions where locoregional therapies like RFA have had diminished efficacy rates.[4] The rate of local tumor progression increases rapidly when tumor diameter exceeds 3 cm.[5,6] In tumors >5 cm treated with RFA alone, follow-up imaging reveals coagulative necrosis of large lesions varying between 29% and 70%.[4] Not only is there diminished local control but residual microscopic nests of tumor may result in local tumor progression, which can lead to microscopic vascular invasion or satellite lesions, which are accurate predictors of distant intrahepatic recurrence after curative local therapy.[7,8]

Failure to achieve durable local control with thermal ablative techniques is in part attributed to the perfusion-mediated heat-sink effect. Convective cooling by hepatic blood flow limits maximal thermal coagulation and therefore tumor kill in the ablation zone, and it has been observed adjacent to vessels as small as 3 mm.[9] It is the core factor limiting coagulative necrosis in the bio-heat equation, which was first described by Pennes and provides the fundamental rubric for understanding the basis for thermal ablation in the setting of dynamic factors including blood perfusion,

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electrical conductivity, and sensitivity to heat and other adjuvant chemotherapies.[10] An approximate construal of this equation defines thermal coagulation necrosis as the product of energy deposited and the local tissue interactions of that system minus the heat loss.[11]

The heat-sink effect is the underlying principle for combining vaso-occlusive therapies with ablative techniques. Among the locoregional therapies available for patients with unresectable HCC, chemoembolization is the most frequently used treatment option and the standard of care for patients with adequately preserved liver function and performance status.[12] Lipiodol chemoembolization is the best represented of the embolic techniques in the literature, with proven survival benefit. Lipiodol chemoembolization involves selective catheterization with intra-arterial administration of a chemotherapy emulsion followed by arterial embolization, and it achieves >60% 1-year and 30% 3-year survival in patients with HCC >5 cm in size.[13] Although chemoembolization may promote robust disease control, it has not routinely demonstrated complete necrosis in tumors >3 cm, and less so in those >6 cm.[14]

In an effort to promote more durable local control of larger lesions, thermal ablation has been combined with chemical ablative techniques and with vaso-occlusive procedures such as chemoembolization and bland embolization in an effort to mitigate the limitations inherent in the use of any single treatment for HCC >3 cm. Tumors >3 cm were shown by Yao and colleagues to be nine times more likely to progress than smaller tumors, which is problematic for patients awaiting liver transplants.[15] Analysis of the United Network for Organ Sharing (UNOS) database reveals that one important independent risk factor for candidates with HCC dropping off the waiting list are maximum tumor size.[16] Combination therapies do present viable options for abrogating tumor progression and potentially downsizing tumors to facilitate transplant.[17] The most studied combination therapies include chemoembolization with RFA and chemoembolization with percutaneous ethanol injection (PEI), which have shown complete response rates ranging from 67% to 90% for tumors >3 cm.[18–20] We discuss the two most commonly used combination locoregional therapies and the evidence defining the best techniques in practice.

Combination Locoregional Therapies

Radiofrequency Ablation and Chemoembolization

RFA combined with chemoembolization is the most studied combination therapy used to treat hepatic malignancies. The value of combining thermal ablation with locally administered chemotherapy was demonstrated by Goldberg et al, who showed that RFA and direct intratumoral injection of doxorubicin markedly increases the extent of induced coagulation, and that intravenous administration of liposomal doxorubicin boosts the effectiveness of RFA in both an animal model and in human hepatic tumors.[21,22]

The rationale for combining thermal ablation with chemoembolization is twofold. The occlusion of the hepatic artery and cessation of blood flow in the treatment zone decreases perfusion-mediated tissue cooling, reducing the heat-sink effect. This increases the lethal thermal coagulation zone. In addition, a larger volume of sublethal hyperthermia is exposed to synergistic high concentrations of chemotherapeutic drugs, particularly doxorubicin.[7,23] This synergy occurs through multiple mechanisms including increased cellular membrane permeability, improved intratumoral accumulation of chemotherapy, and increased cytotoxic drug sensitivity due to the dismantling of adenosine triphosphate–driven multidrug-resistant mechanisms. The increased volume of coagulative necrosis including the lethal and sublethal hyperthermic zones widens the ablation margin, destroying microscopic satellite lesions adjacent to the central tumor, ultimately improving local control.[21,24,25]

Percutaneous Ethanol Injection and Chemoembolization

PEI is widely used for ablation of small HCC due to its safety, ease of use, low cost, and efficacy. Ethanol injected into a tumor induces coagulation necrosis through multiple mechanisms including cellular dehydration, protein denaturation, and thrombosis of microvasculature. Ethanol selectively permeates the tumor vasculature while the surrounding firm cirrhotic liver reduces washout.[26]

Although PEI is an effective local ablative technique for HCC <2 cm, like RFA it has challenges in inducing durable local control for larger tumors. This limitation relates to failure to routinely affect complete tumor necrosis due to the inhomogeneous distribution of ethanol through the lesion, particularly in those with intratumoral septa. Another limitation is the inability to generate safety margins of ablation in the liver parenchyma surrounding the tumor, which fails to kill the surrounding daughter tumor foci. These satellite lesions occur more often as tumor diameter increases and are usually not seen on pretreatment imaging.[27]

Chemoembolization can be used synergistically with PEI. It is postulated that although the visible tumors are ablated by PEI, microscopic metastases are destroyed by chemoembolization. In addition, chemoembolization is thought to result in the lysis of intratumoral septae and the formation of a fibrous wall around the hypervascularized tumors, which ultimately results in more homogeneous distribution of ethanol with the subsequent PEI.[28] By pretreating lesions with a combination of chemoembolization and repeated PEI, it is thought that peripheral micrometastases are better controlled, greater diffusion of ethanol is facilitated, and complete necrosis is promoted resulting in more effective tumor kill.[29,30] In cases of hypovascular tumors where isolated treatment with chemoembolization is less effective, the combination of PEI following chemoembolization is thought to be more effective.

One consideration when combining chemoembolization with thermal ablative techniques is that the efficacy of certain chemotherapeutic drugs, including doxorubicin and mitomycin, is diminished when exposed to maximal ablation temperatures. However, drug inactivation occurs only at lethal temperatures, at which point tumors cells are already killed, so this has little impact on such combination therapies.[31]

RFA versus PEI

RFA is widely touted as the best ablative technique for HCC, with five randomized controlled trials (RCTs) defining RFA as superior to PEI in providing better local control.[32–36] However, the survival advantage of RFA over PEI has been a point of dispute. The three RCTs conducted in Asia have shown survival benefit, the two European RCTs do not demonstrate a statistically significant difference in survival outcomes. Nevertheless, three meta-analyses evaluating these RCTs conclude RFA has a survival benefit over PEI, chiefly among lesions >2 cm.[37–39] However, in locations where thermal ablation poses risk of severe complications and/or suboptimal treatment, such as adjacent to critical structures or large vessels, PEI is the preferred treatment.

Treatment and Technical Approach

Patient Selection for Combination Therapies

Combination therapy with chemoembolization and RFA or PEI is an option for patients with HCC who present with a single medium- or large-size tumor (>3 cm, <8 cm), well-preserved liver function (Child-Pugh A or B), and good performance status (Barcelona Clinic Liver Classification [BCLC] A–C, Eastern Cooperative Oncology Group [ECOG] 0–2). These may be persons currently on the liver transplant list with a protracted waiting time or may be nonsurgical candidates. The decision to perform combination therapy with PEI versus RFA is often based on tumor location, with RFA offered preferentially to those that are technically accessible and PEI reserved for those adjacent to critical structures or near the hepatic hilum.

The presence of adequate liver function is critical to consider when balancing the risk of treatment-induced liver failure with the potential cytoreductive or survival benefit from the tandem intervention. This relates primarily to the chemoembolization aspect of the combination therapy, where patients present with certain high risk factors such as serum bilirubin >2 mg/dL, lactate dehydrogenase >425 U/L, aspartate aminotransferase >100 U/L, and tumor burden that involves >50% of the liver. Other relative contraindications include extrahepatic metastasis, poor performance status (ECOG >2), cardiac or renal insufficiency, ascites, encephalopathy, recent variceal bleeding, uncorrectable coagulopathy, intractable arteriovenous fistula with shunting through the tumor, intractable systemic infection, and Child-Pugh C liver disease.[40] Of note, in a comparison of 12 liver staging systems, Child-Pugh nominal staging system was the most accurate in predicting survival of patients with unresectable HCC treated with chemoembolization. Although absence of hepatopetal blood flow was historically considered an absolute contraindication, various articles have demonstrated that hepatic function may not be compromised if selective chemoembolization is performed in the setting of portal vein obstruction secondary to tumor thrombus.[41,42]

Patient Preparation

Patients should receive dynamic triphasic computed tomography (CT) or magnetic resonance (MR) imaging to assess for the presence of extrahepatic disease and also define tumor burden and viability. Once combination therapy is deemed appropriate, the presence of macrovascular invasion, biliary obstruction, celiac stenosis or occlusion, and variant vascular anatomy is assessed to guide embolization treatment planning. On the day of therapy, patients are vigorously hydrated and given antiemetics; many operators use antibiotic prophylaxis, although this practice is not evidence based.

Embolization: Selective mesenteric portography is performed for vascular mapping to assess for variant anatomy and to assess patency of the portal vein. Selective hepatic angiography may then be achieved using a standard diagnostic catheter or a coaxial system. Prior to treatment, intra-arterial lidocaine may be administered. Bland embolization (with 40- to 300-μm microspheres) or chemoembolization may then be performed that may involve a mixture of mitomycin C (e.g., 50 mg/m^2), doxorubicin (e.g., 50 mg/m^2), 5 to 20 mL Lipiodol, and/or drug-eluting microspheres. Upon achieving stasis or reflux into the portal system, the injection is halted. Once embolization is complete, a control angiogram is performed to document the extent of compromised hepatic arterial perfusion and the degree of diminution of tumor vascularization. The patient is admitted overnight for post-procedural monitoring and medical management.

PEI: PEI is performed 2 to 6 weeks after transarterial chemoembolization, allowing for interval necrosis of intratumoral septations. PEI is administered under ultrasound guidance with a treatment schedule that on average includes four to six sessions, performed once or twice weekly. Some centers offer intravenous infusions of antibiotics and fluid replacement 2 days before and 2 days after PEI. At each session, patients undergo a focused abdominal ultrasound examination to evaluate for ascites and to coordinate the best access path to the tumor that avoids large vessels. Although PEI may be performed under local anesthesia and moderate sedation, single-session techniques under general anesthesia for large tumors have been used with reduced pain and patient movement.[43] Single-session therapy has also extended the range of treatable tumors.

After pretreatment to minimize discomfort (e.g., 0.1 mg fentanyl and 1.25 mg droperidol) or sedation with anesthesia, a local anesthetic should be given (e.g., 0.5% lidocaine hydrochloride) and a skin incision ~5 mm wide is made. Conventional technique characteristically involves the use of a blind-ended straight needle such as a 21-gauge diamond-tip needle with three side holes. However, in light of a recent animal study by Kawamura et al, the use of a multipronged needle was found to substantially increase the volume of coagulation when compared with the conventional technique with the straight needle.[28] The multipronged injection needle includes an 18-gauge puncture needle 20 cm in length and a skin guide with a 30- and 60-degree reference chart. The needle has three retractable prongs, each of which has four terminal side holes, and it also bears a connector with extension tubing clamp. The deployment of prongs occurs through the lateral wall of the needle (1.5 cm proximal to the needle tip) with a maximum deployment distance of 5 cm. Ethanol is manually injected through the syringe that connects via tubing to the

handle as the prongs are slowly withdrawn to distribute the ethanol. The needle is rotated 60 degrees and the prongs redeployed for a second injection.

Beginning at the most distal part of the tumor, ethanol is continuously injected while cautiously retracting the needle until the tumor echogenicity becomes homogeneous. The use of ultrasound guidance is vital for real-time monitoring of the injection of ethanol and also to monitor for inadvertent spillage of ethanol outside the lesion into the diseased liver or back along the needle track to the peritoneum. Careful assessment to determine the presence of homogeneous diffusion of ethanol both into the center of the lesion and into the immediate periphery is critical. In cases where ethanol seeps into blood vessels or adjacent liver parenchyma, injection should be discontinued and the tines withdrawn and needle shaft rotated around its axis to reposition for reinjection. Appropriate diffusion of ethanol within the tumor should be confirmed. In instances where ethanol diffusion is seen to be inadequate, tines should be retracted and the needle shaft retracted 1 to 2 cm followed by redeployment.

Although in practice ethanol is administered until there is a homogeneous change in echogenicity of the treated region, the guideline for the requisite volume of injected ethanol is calculated according to the formula $V = 4/3\ \pi(r + 0.5\ cm)^3$, where V (in milliliters) is the ethanol and r is the radius for the tumor (in centimeters); 0.5 cm is added to help promote a peritumoral ablative margin of safety.[43] In the past, the amount of ethanol that could be applied during a single session was limited. However, there has been an advancement in technique through the introduction of the single-session high-dose technique under general anesthesia by Livraghi and colleagues. Here, the administration of larger volumes of ethanol during one session under mechanical ventilation has allowed for the treatment of larger tumors and more lesions at one time, requiring fewer interventions.[43,44] Moreover, the use of mechanical ventilation has facilitated access for technically difficult areas during deep inspiration (e.g., liver segments 1, 2, or 8).

A dynamic CT or dynamic MR scan may be performed 3 to 7 days postprocedure to determine if complete necrosis has been achieved, which is defined as tumor and surrounding tissue that fails to demonstrate enhancement in the arterial and portal phase. If residual tumor vascularization is noted, additional PEI treatment may be initiated. Given the uneven distribution of the liquid ethanol within the solid tumor, multiple injections are usually necessary. In the event of no detectable tumor vascularization, patients may then be followed up quarterly.

Thermal ablation: To take advantage of the synergies with chemoembolization-induced ischemia and drug deposition, thermal ablation should be performed within 24 hours of arterial therapy. There are numerous devices using RFA, microwave, or laser energy for percutaneous ablation that are employed according to the manufacturer's directions. Because thermal ablation is much more painful and prolonged than PEI, deep sedation or general anesthesia is required. Ultrasound guidance is convenient for initial probe placement, but gas generated during the ablation obscures the target. If Lipiodol is used during chemoembolization, the oil makes a conspicuous target under ultrasound, CT, or even fluoroscopy. CT allows for accurate depiction of probe position and facilitates multiple or overlapping burns. Thermal energy can be used to ablate the probes tract during withdrawal to minimize risk of bleeding or tumor seeding.

Technical Considerations

Order of embolization: The order in which combination therapy occurs varies among interventionalists. Although the embolization of tumor blood supply followed by thermal ablation seems intuitively to be the ideal way to combat the heat-sink effect, an alternative approach is to ablate first. In a rabbit model of HCC, the difference in the size of the coagulum produced by chemoembolization followed by RFA versus RFA followed by chemoembolization was not statistically significant.[45] It is hypothesized that initial ablation induces coagulation of the relatively poorly perfused tumor core with intense perilesional hyperemia resulting in improved uptake and retention of the subsequently injected chemoembolic emulsion.

There is no consensus about the optimal time period between the different components of any combination of therapies. We perform RFA 1 day after the chemoembolization, whereas other centers have reported separating the components of combination therapy by up to 2 weeks. No data have clearly defined the optimal time window. Performing RFA the day after chemoembolization partly stems from a desire to take advantage of maximal local drug concentrations for hyperthermic synergy. Moreover, considering that patients are admitted following chemoembolization, it is convenient to perform RFA the following day.

Assessing Efficacy of Combination Locoregional Therapies

In light of the absence of randomized prospective trials and the variations in cohort design, it is difficult to reliably compare disease control and survival rates among patient series in the literature. Despite this issue, there appears to be improved local control and some survival benefit for chemoembolization-PEI and chemoembolization-RFA regimens when compared with single independent use of each modality when targeting liver tumors >3 cm.

In the case of PEI, the major limitation has been its high local recurrence, which has been reported as high as 33% in lesions <3 cm and 43% in those >3 cm.[46,47] Part of this issue relates to the inhomogeneous ethanol distribution, its limited treatment of extracapsular spread, and the fact that even in 30% of small HCCs, there are also small microscopic intrahepatic metastatic foci that may be undertreated by PEI.[48] Since 1991, when chemoembolization was initially combined with PEI to assist in improving local control, superior results have been demonstrated when compared with either chemoembolization or PEI used alone. Enhanced survival benefit has been demonstrated from combined PEI and chemoembolization by several studies. In a study by Bartolozzi et al that used chemoembolization alone or PEI plus chemoembolization to treat patients with mean tumor sizes of 4.8 cm and 5.1 cm,

respectively, there were superior recurrence-free survival rates (100% and 72% after 1 and 2 years) compared with repeated chemoembolization alone.[49] Allgaier et al also treated lesions, 95% of which were >3 cm, and they demonstrated a survival benefit in patients stratified to a combination of chemoembolization plus PEI versus PEI alone, primarily due to a decreased recurrence rate.[50]

In a study by Dettmer et al, where tumors with a mean size of 5.3 cm were treated, groups receiving combined chemoembolization and repeated single-session PEI were compared with those receiving repeated single-session PEI, repeated chemoembolization, and best supportive care. Here, there was a 1-, 3-, and 5-year survival probability of 90%, 52%, and 43%, respectively, after initial stratification to chemoembolization followed by PEI, respectively, and survival probabilities of 65%, 50%, and 37% after PEI alone. Furthermore, in a group of 10 patients with >7 cm or multiple ($n > 5$) tumors, who were switched from the repeated chemoembolization group to secondary PEI after being reevaluated, there were 1-, 3- and 5-year survival rates of 91%, 40%, and 30%, respectively.[48] In a randomized study by Koda et al that treated tumors with an average size <3 cm, superior survival rates were again demonstrated. For the combination therapy group, it was 100%, 80.8%, and 40.4% at 1 year, 3 years, and 5 years, respectively, versus 91.3%, 65.9%, and 37.7%, respectively, for the group undergoing PEI alone.[51]

In the case of RFA combined with chemoembolization, the rate of local tumor progression increases rapidly when tumor diameter exceeds 3 cm, with the 2-year local progression-free survival rate after RFA reported at 74.1% for small (<3 cm) HCCs but only 38.3% for medium (3 to 5 cm) and large (5 to 7 cm) HCCs.[7,52] Similarly, in a large prospective series of patients treated with chemoembolization alone, rates of complete necrosis for tumors 3 to 5 cm were 50 to 68%; for tumors >6 cm, the rate was 13%.[53] However, in the case of RFA and chemoembolization, the enhanced efficacy does not seem to be seen when treating smaller HCCs, where comparable local control rates for chemoembolization combined with RFA were demonstrated when compared with RFA alone.[7] Although the coagulum from RFA alone may provide ample local tumor control, the limitation of this combination may relate to the inherent limitation of chemoembolization on these small lesions.[54] For example, in HCCs >1.5 cm, which bear fewer portal tracts but contain more intralesional arterioles, there is less dependence on hepatic arterial blood flow and more resistance to chemoembolization.[55]

Few studies have evaluated the role of combination therapy in intermediate to larger size tumors. In a 2010 RCT by Morimoto et al, which combined RFA with chemoembolization for treating patients with intermediate-size (3.1 to 5.0 cm) HCCs, there was a significantly decreased tumor progression rate in the chemoembolization and RFA-treated group when compared with the RFA-only treated group (6% versus 39%; $p = 0.012$). The 1-, 2- and 3-year survival rates of patients in the RFA group were 89%, 89%, and 80%, respectively; in the chemoembolization-RFA group, they were 100%, 93%, and 93%, respectively. However, there was no significant difference in survival between the two groups (log-rank test; $p = 0.369$).[56]

In a retrospective study by Kim et al evaluating combination chemoembolization-RFA for intermediate-size tumors versus RFA alone, local tumor progression was observed in 40% of treated lesions in the former versus 70% in the latter group. There were also significantly decreased rates of local tumor progression at 1, 3, 5, and 7 years in the chemoembolization plus RFA group (9%, 40%, 55%, and 66%, respectively) versus those seen in the RFA-alone group (45%,76%, 86%, and 89%, respectively; $p < 0.001$).[52]

Similar improved survival rates are reported in the case control study by Peng et al, where tumors >5 cm receiving combination therapy were compared with those treated with RFA alone.[57] Smaller case series report 1-year survival rates >95%.[22,26] In a study by Maluccio et al, where 33 patients were treated with a combination of bland arterial embolization and ablation for single HCC up to 7 cm (median: 4 cm), 1-, 3-, and 5-year survival rates of 97%, 77%, and 56%, respectively, were reported.[58]

Future Considerations for Combination Therapy

Given that chemoembolization is the principal therapy for solitary lesions <8 cm or multinodular tumors (>3-cm lesions) without extrahepatic disease and well-preserved liver function, this therapy represents the hub for combination therapies in this challenging group.[59] As a result, sufficient attention should be given to developing an optimized chemoembolization regimen that heightens persistence of maximal chemotherapeutic concentrations intratumorally with minimal systemic drug delivery. Historically, due to suggestions of increased risk of chemoembolization-associated complications in patients with greater disease burden necessitating nonselective embolization who may have unfavorable anatomy and limited liver function, chemoembolization has not been routinely offered to such patients.[60] However, given the proven efficacy of chemoembolization with drug-eluting beads and its gentler side-effect profile, consideration can now be made for combining it with thermally ablative techniques like RFA and microwave ablation for patients with more advanced disease. Here, such patients with Child Pugh B, ECOG 2, BCLC C, bilobar or recurrent disease, or those with mild to moderate cardiac failure have generally been considered less than ideal candidates for the studied conventional chemoembolization-based combination regimens; these patients now represent a potentially favorable group to be studied in light of the results of the PRECISION V trial.[61]

Given that the basis for chemoembolization involves the local induction of tissue hypoxia that in turn increases vascular endothelial growth factor (VEGF) levels, combining chemoembolization with adjunct anti-VEGF therapies represents an arena with potential promise.[62] Sorafenib, which is a multikinase inhibitor with antiangiogenic and antiproliferative properties, has been considered the therapy of choice for patients with advanced HCC, with two RCTs demonstrating prolongation of median survival and median time to radiologic progression when compared with placebo.[63,64] The

benefit of combining sorafenib and the drug-eluting beads in chemoembolization for patients with advanced liver disease has been validated and represents an area of great promise. The determination of the optimal formulation of chemoembolization with RFA represents ongoing research and is the basis for a phase 2 randomized double-blinded placebo-controlled trial that is studying the safety and efficacy of thermally sensitive liposomal doxorubicin (ThermoDox) in combination with RFA for nonresectable HCC.[65]

Conclusion

HCC represents a challenge in oncologic management, with few patients presenting as candidates for surgical resection or transplantation, and those with "curative" resections often experiencing metachronous recurrence of HCC in their diseased liver. Similarly, although liver transplantation represents the best option for cure or long-term survival and treats both the tumor and underlying cirrhosis, only a small fraction of patients fall within the Milan or San Francisco transplantation criteria. Furthermore, even in those patients successfully transplanted, the risk of HCC recurrence or extrahepatic disease persists. As a result of such challenges, combined locoregional therapies have represented a powerful and well-respected therapeutic option for clinicians battling HCC.

The most studied combination locoregional therapies include RFA with chemoembolization and PEI with chemoembolization. These combinations have proven to be viable treatment options for patients presenting with single medium- or large-size tumors (>3 cm, <8 cm), well-preserved liver function (Child-Pugh A or B), and good performance status (BCLC A–C, ECOG 0–2). Within this group, the intermediate-size HCCs have been the lesions most amenable to local control by the therapies just mentioned. Unfortunately, patients with tumors >5 cm are a particularly challenging group where combined locoregional therapies render little benefit. To further define the optimal strategy for this group and those with advanced disease, current research has explored combination treatments that include RFA or chemoembolization followed by systemic treatment with sorafenib, bevacizumab, and tumor-specific agents such as 3-bromopyruvate. As continuing research focuses on refinements of thermal ablative treatments like microwave ablation and RFA, the modification of chemoembolization with chemotherapy eluting beads, bioabsorbable beads, and others, as well as better targeted chemotherapy, is likely to yield an improved survival benefit. In any event, locoregional combination therapies form a critical pillar in the care of these patients, the wealth of combinations of which have yet to be explored.

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