Enhancing Ablation: Synergies with Regional and Systemic Therapies

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Ablative therapies often achieve complete response in solid tumors smaller than 3 cm, but local control becomes rapidly less common with increasing tumor diameter. Combining treatment modalities can increase the local control rate for larger tumors. Demonstrating the value of this is not straightforward. The prognosis of patients with higher-stage disease may not be improved by better control of their index tumor if their natural history is progression of disease at other sites. Combination therapies will need prospective evaluation for each tumor type and stage in randomized trials to elucidate the role of integrated therapies in global cancer care.

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Abbreviations: HCC = hepatocellular carcinoma, PMCT = percutaneous microwave coagulation therapy, RF = radiofrequency

SUCCESSFUL percutaneous thermal ablation of solid tumors is dependent on a number of factors, including the amount of heat deposited, the thermal conductivity of the tissue, and the heat lost through adjacent blood vessels that act as "heat sinks" (1). Thermal ablation of tumors less than 3 cm in diameter results in complete necrosis 76%–100% of the time, but the incidence decreases to 29%–48% for diameters greater than 3 cm (2). Even among tumors initially deemed radiographically to show complete necrosis, local progression may be detected on follow-up imaging as long as 1 year later (3). Such limitations in thermal ablation have led investigators to combine it with other treatment modalities.

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COMBINATION THERAPIES IN THE LIVER

One of the most commonly addressed shortcomings in thermal ablation is the heat lost through blood flow. Vessels as small as 3 mm provide sufficient thermal loss to limit the zone of lethal coagulation (3). Many methods have been used to reduce the amount of convective heat lost as a result of blood flow. One of the first was stopping blood flow in the hepatic artery by balloon catheter occlusion or with gelatin sponge pledgets (1). Occlusion of tumor arterial supply resulted in almost doubled diameter of coagulation necrosis, from 2.5 cm without occlusion to 3.5–5.5 cm with occlusion. Among 62 solitary hepatomas with a mean diameter of 4.7 cm (range, 3.5–8.5 cm), complete ablation by imaging criteria was achieved with a single treatment session in 90% of cases and in 100% of cases with a second session, with a local progression rate of 19% at 1 year. These results strengthened the premise that cooling from hepatic artery blood flow hampered cell death adjacent to vascular structures.

Many investigators followed suit by combining thermal ablation with chemoembolization (2,4,5). This combination provides multiple synergistic effects. Embolization reduces hepatic arterial blood flow and thereby perfusion-mediated heat loss. When the chemoembolization is performed before thermal ablation, high concentrations of cytotoxic drug(s) are present in the tumor and surrounding tissue. The hyperthermia around the central zone of thermal coagulation acts synergistically to increase drug uptake and cytotoxicity (6). The enhanced diameter of drug- and coagulation-induced necrosis increases the tumor-free margin by killing microsatellite lesions and venous tumor emboli surrounding hepatocellular carcinoma (HCC) lesions, thereby decreasing marginal recurrence.

Several recent studies (5,6) have analyzed the efficacy of combined treatments of radiofrequency (RF) ablation and chemoembolization based on the size of the lesion. These studies have shown 5-year survival rates of 41% for lesions greater than 5 cm and 75% for lesions less than 5 cm. This can be compared to 5-year survival rates as low as 8% in lesions 5 cm or smaller with chemoembolization alone and 38% for lesions smaller than 5 cm with RF ablation alone (3,7). The 5-year survival rates after combined therapy are comparable to those for hepatic resection, which are 75% and 81%, respectively (5). The recurrence-free survival rates for patients with lesions smaller than 5 cm were also very similar, at 27% and 26% in the combination and hepatectomy groups, respectively (5).

Based on the literature, the improved survival and decrease in local progression after combined therapy for lesions larger than 3 cm is very strongly supported. However, combined treatment for lesions smaller than 3 cm seems to be associated with similar 5-year survival and local progression–free survival rates compared with RF ablation alone (8,9). This suggests that there is no added benefit from embolizing smaller tumors, reflecting the excellent tumor control achieved by ablation alone. Another theory for the reduced effect of embolization on tumors smaller than 3 cm is based on the histologic finding that the number of intratumoral portal tracts in HCC decreases significantly and the number of intratumoral arterioles increases significantly when the greatest dimension of an HCC exceeds 1.5 cm (10). Therefore, blocking the arterial supply with chemoembolization may be most useful for larger lesions that have greater arterial supply than for smaller lesions that have less arterial blood supply.

The order of procedures—chemoembolization followed by ablation or vice versa—is practitioner-dependent. Most commonly, chemoembolization is performed first as a result of the benefits of reducing blood flow and the synergy between hyperthermia and doxorubicin chemotherapy. When chemoembolization is performed on an inpatient basis, performing ablation the next day before discharge is a practical and efficient use of resources. Bench-top studies have demonstrated that the efficacy of chemotherapeutic drugs such as doxorubicin and mitomycin is lost when they are exposed to the high temperatures seen during thermal ablation (11). The clinical impact of this is negligible, as drug inactivation occurs only at lethal temperatures and not under conditions of sublethal hyperthermia at which the synergy occurs (12). A practical concern is that chemoembolization adversely affects the quality of ultrasound imaging used for ablation because the lesions become hyperechoic, thereby obscuring electrode placement and contrast enhancement used to identify viable tumor (13). Computed tomographic images are similarly obscured by iodized oil in the lesion (13).

A number of reports (5,6,9) have shown that the major complication rate is less than 3% in combination chemoembolization and in ablation alone. Major complications were often caused by the ablation and included pseudoaneurysm, subcapsular hemorrhage, diaphragmatic perforation, liver abscess, and most commonly pneumothorax (9).

Combination of Chemoembolization and Percutaneous Microwave Coagulation Therapy for HCC

Microwave ablation is another method of thermal ablation that may offer several advantages compared with other methods. Microwaves, unlike RF, penetrate through dehydrated and charred tissue and produce temperatures much greater than RF (13,14). One of the major shortcomings of microwave ablation is the inability to treat large tumors without numerous overlapping ablation procedures (15). A number of trials have been conducted combining percutaneous microwave coagulation therapy (PMCT) with chemoembolization to minimize the shortcomings of PMCT (16,17). Chemoembolization can act synergistically with PMCT by reducing arterial blood flow, thereby reducing the cooling effect. PMCT procedures are often performed 2 days to 2 weeks after chemoembolization to maximize the degree of tissue ischemia and inflammatory edema. Some patients in the studies required more than one PMCT treatment for an adequate ablation margin to be adequately achieved. Studies combining the two treatments on lesions smaller than 3 cm, with follow-up between 6 and 31 months, showed no local progression in 94% of patients (17,18).

No fatal complications were observed in the combination group compared with either therapy alone (16,17). Side effects in the combined treatment group included pain and fever, with only one case of pleural effusion, but no internal bleeding, subcapsular hematoma, or biliary duct damage were seen.

Chemoembolization before Interstitial Laser Ablation in Liver Cancer

Several studies have combined the use of chemoembolization with interstitial laser ablation for primary and metastatic malignancies to manage lesions too large for interstitial laser ablation alone (16,19). The rationale for the use of chemoembolization before interstitial laser ablation is twofold. The use of chemoembolization decreases the size of the tumor and reduces vascular flow, allowing optimal treatment by interstitial laser ablation, and interstitial laser ablation ablates remaining viable cells in large lesions after chemoembolization treatment. Neoadjuvant downsizing of tumors with chemoembolization was done in a study of patients with metastatic liver tumors ranging in diameter from 5 cm to 8 cm (16). An average of 4.3 chemoembolization procedures were required per patient to reduce tumor size by approximately 35%. After a reduction in tumor size, each patient received an average of two interstitial laser ablation procedures. The cumulative survival in the combined therapy was 26.2 months, compared with 12.8 months in patients who did not receive interstitial laser ablation (19). A similar methodology has been used in other studies on primary HCCs 5–8 cm in diameter, with an average of 3.5 chemoembolization treatments per patient reducing tumor size to less than 5 cm in 66% of the patients (20). Four to 6 weeks later, interstitial laser ablation was preformed an average of 1.9 times per patient who showed a response to chemoembolization, resulting in a mean survival time of 36 months. The remaining 33% of patients did not have a reduction in tumor size or had disease progression.

Complications of the combined procedure were mild and well tolerated. Approximately 8.5%–30% of patients experienced pleural effusion or subcapsular hematoma after the interstitial laser ablation treatment that resolved spontaneously. In one study (19), there were three incidents of embolization of nontargeted areas that did not result in any long-term sequelae.

Chemoembolization with Cryoablation for Liver Cancer

Cryoablation can be combined with chemoembolization to reduce the local progression of a malignancy. This therapy was compared with cryosurgery alone retrospectively in a group of patients with HCC (21). During a mean follow-up of 42 months, the local progression rate was 11% for sequential combined therapy compared with 23% for cryosurgery only. The 5-year survival rate was higher for the combined