Combination Percutaneous and Intraarterial Therapy for the Treatment of Hepatocellular Carcinoma: A Review

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ABSTRACT

Transcatheter arterial chemoembolization (TACE) and percutaneous ablation therapies have been shown to provide effective therapy and afford survival prolongation for patients with unresectable hepatocellular carcinoma (HCC). Both treatments, however, have inherent limitations that restrict their benefit; TACE is not a curative therapy and ablation efficacy is significantly limited by lesion size. Current treatment strategies aim to combine intraarterial and percutaneous liver-directed therapies synergistically to improve tumor response, and by extension improve patient survival. This article reviews the current literature on combination treatments, and examines the circumstances in which therapeutic combinations would improve tumor response and patient survival.

KEYWORDS: Hepatocellular carcinoma, chemoembolization, radiofrequency ablation, cryoablation, microwave

Objectives: Upon completion of this article, the reader should be able to explain the rationale and role for combining intraarterial and percutaneous ablative therapies to improve tumor response and patient survival, and should also be able to identify the circumstances in which therapeutic combinations should be considered in the treatment of liver cancers.

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Hepatocellular carcinoma (HCC) is the eighth most common malignancy worldwide,¹ with a median survival of 3 to 9 months for unresectable disease.² Areas of high prevalence include sub-Saharan Africa and Southeast Asia where a large portion of the population is infected with the hepatitis B virus (HBV), the factor most strongly associated with the development of HCC.¹ Though HCC is not as common in the United States, its incidence has increased by 70% in the last

20 years.¹ This is attributed to a threefold increase in the incidence of hepatitis C virus (HCV) liver disease between 1993 and 1998 and to a marginal increase in the incidence of HBV and alcoholic cirrhosis, a trend that is expected to continue.³ Although surgery may be the only chance for cure, less than 15 to 20% of patients are considered resectable at presentation,^{4,5} and even among these, the 1- and 5-year survival rates are only 55 to 80% and 25 to 50%, respectively.⁵ Additionally,

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perioperative mortality is relatively high (15 to 30%) due to the limited liver functional reserve of these patients.⁵ More than 90% of HCCs occur in the setting of underlying liver cirrhosis,⁶ which predisposes the patients for the development of metachronous foci of HCC, seen in at least 75% of postresection patients.⁷ Transcatheter arterial chemoembolization (TACE) has become the mainstay of treatment for patients with unresectable HCC. The pivotal studies of Llovet,⁸ Lo,⁹ and Camma¹⁰ established the survival benefit of TACE and helped cement it as the most common treatment for such patients. Less commonly used locoregional treatment options include ablative techniques. Of these, radiofrequency ablation (RFA) is the most widely used, both in the open operative setting and percutaneously, with microwave ablation and cryoablation less commonly utilized. Combination treatments using both intraarterial liver-directed therapy and percutaneous ablation seek to overcome the disadvantages of the individual treatments alone, theoretically improving response to therapy and survival. For example, though ablations are considered curative options in selected patients, efficacy is severely limited by lesion size. On the other hand, though TACE is not limited by lesion size and usually results in good tumor response, it is not considered a curative option. Both treatments have independently been shown to prolong survival in patients with unresectable HCC. It is reasonable therefore to expect the combination of percutaneous and intra-arterial therapies would improve tumor response, and by extension improve patient survival. In this article, we review the current literature on combination treatments, including TACE and RFA, TACE and microwave ablation, and TACE and cryoablation, and examine the clinical circumstances in which these therapeutic combinations would improve tumor response and patient survival.

TACE AS MONOTHERAPY

Because TACE is the current standard of care for unresectable HCC and the treatment to which other therapies are compared, it is fruitful to establish its efficacy and safety.

TACE EFFICACY

In the first published randomized controlled trial comparing TACE to best supportive care, Lo et al reported the 1-, 2-, and 3-year survival of patients with unresectable HCC to be 57%, 31%, and 26% in the treatment group versus 32%, 11%, and 3% in the control group ($p=0.002$).⁹ In a review of trials, Llovet and Bruix reported that such patients treated with TACE had a significantly longer 2-year survival than controls (odds ratio = 0.53; 95% confidence interval = 0.32–0.89;

$p=0.017$).⁸ Finally, in a meta-analysis, Camma et al concluded that TACE significantly reduced the 2-year mortality rate (odds ratio = 0.54; 95% CI = 0.33–0.89; $p=0.015$) compared with controls.¹⁰ Additionally, response to TACE seems to be strongly associated with a better outcome, which some authors attribute to an indication of better tumor biology.¹¹ The utility of TACE as a bridge to liver transplantation has also been investigated. One study showed similar disease-free survival between patients who became transplant candidates after they were downstaged as a result of TACE versus patients that were already transplant candidates (93.3%, 82.5%, and 82.5% at 1, 3, and 5 years, respectively).¹²

TACE SAFETY

The most commonly reported complication of TACE is termed “postembolization syndrome,” which is comprised of abdominal pain, nausea, and fever. This can affect up to 70% of patients. Symptomatic relief has been achieved with intravenous hydration, pain control, and antiemetic medication. Child-Pugh C and Eastern Cooperative Oncology Group (ECOG) performance status 3 are relative contraindications to TACE, and are predictors of poor outcome after treatment. Patients with advanced liver disease may not have enough liver function to sustain injury during TACE, which results in a higher risk of acute liver failure and death.^{13,14} Intrahepatic abscess is more likely if a patient has sphincter of Oddi compromise (due to surgical hepaticocolostomy or sphincterotomy) with a reported risk of 30 to 80%.¹³ Nontarget vessel embolization is a rare but serious complication. Even though most patients can be discharged home on the same day as TACE, most can benefit from overnight aggressive symptomatic treatment for pain, nausea, and fever. Overall, the mortality of TACE is less than 1% for Child-Pugh A or B disease, and has a clinically significant complication rate of 5 to 7%.

COMBINATION TACE AND RFA

RFA has repeatedly been shown to be very effective for the treatment of liver tumors that are <3 cm in size,¹⁵ with an excellent complete response rate. As such, RFA is considered a curative option for small HCC. In a prospective two-arm study comparing TACE plus RFA with RFA alone for HCC 3 cm diameter or smaller, Shibata et al showed that there was no benefit to combination treatment over RFA alone,¹⁵ a result that is not unexpected, as RFA alone demonstrates an ~90% complete response rate for HCC smaller than 3 cm. In this study, the 1-, 2-, 3-, and 4-year local recurrence rates were 14.4%, 17.6%, 17.6%, and 17.6%, respectively, in the combined treatment group and 11.4%, 14.4%, 14.4%, and 14.4%, respectively, in the RFA group

Figure 1 Percent risk rates of the local recurrence rate after radiofrequency ablation (RFA; gray) and transcatheter arterial chemoembolization– (TACE–) RFA (black) treatment for small (<3 cm) hepatocellular carcinoma. The differences are not statistically significant; thus, the addition of TACE does not impart benefit. 1-, 2-, 3-, and 4-year local recurrence rates hover around 15% irrespective of treatment. Similar results have been confirmed by other studies. For percutaneously accessible lesions <3 cm, ablation should be the treatment of choice.

(Fig. 1). The corresponding survival rates were 100%, 100%, 84.8%, and 72.7%, respectively, in the combined treatment group and 100%, 88.8%, 84.5%, and 74.0%, respectively, in the radiofrequency ablation group (Fig. 2). No differences were statistically significant. Studies investigating the efficacy of combination TACE and RFA for larger lesions tend to show both a higher rate of complete response and survival benefit. The 1- and 2-year survival rates are reported to stand at 90% and 67% after combination treatment with a complete radiologic response rate of 57% by necrosis criteria.¹⁶ Gasparini et al confirmed that RFA alone is nearly 100% effective for liver lesions 3 cm or smaller.¹⁷ In addition, Gasparini et al showed that the near 100% complete response rate can be extended to lesions of 3 to 5 cm diameter by adding TACE to the patient's treat-

Figure 2 Survival rates of patients with unresectable hepatocellular carcinoma <3 cm treated with combination transcatheter arterial chemoembolization– radiofrequency ablation (TACE–RFA; black) versus RFA (gray) alone. Addition of TACE conferred no survival advantage to treatment. This is expected because the efficacy of RFA for small liver lesions is ~90% and difficult to improve upon.

Figure 3 3-year survival rates for patients with unresectable hepatocellular carcinoma treated with combination transcatheter arterial chemoembolization– (TACE–) ablation. Survival strongly associated with the rate of complete response to initial treatment, with no patients showing only partial response surviving past 3 years. This highlights the importance of achieving a complete response if possible. Combination treatments can increase chances of complete response, especially in patients with 3 to 5 cm lesions.

ment protocol. Radiologic response to locoregional treatment has been associated with better outcome. A combination of RFA followed by TACE has been shown to result in 1-, 2-, and 3-year survival rates of 83.1%, 55.7%, and 43.7%, respectively. Furthermore, subgroup analysis showed that the 3-year survival rate was 78.6%, 28.1%, and 0% for complete ablation, nearly complete ablation, or partial ablation, respectively (Fig. 3).¹⁸ This highlights the importance of trying to achieve complete radiologic response in patients with unresectable HCC. Improved survival with combination TACE–RFA was also suggested by Bloomston et al.¹⁹ In his report, 1-year survival was greater in patients treated with TACE–RFA than with TACE alone (100% versus 67%, $p=0.04$). Mean survival was also longer after TACE–RFA compared with TACE alone (25.3+/-15.9 months vs 11.4+/-7.3 months, $p<0.05$).

TACE–MICROWAVE ABLATION

As with RFA, microwave ablation exhibits very high complete response rates for liver lesions smaller than 3 cm. A near 100% complete response rate is noted for lesions 2 cm or smaller. The complete response rate drops to ~50% for lesions as large as 6 cm in diameter.^{20,21} Thus, the combination of microwave ablation and TACE remains of questionable added benefit for lesions <3 cm. Nonetheless, in a study limited to lesions smaller than 3 cm, Wei-Zhu et al showed a 100% 1-year survival rate and a 5% local recurrence rate.²² Near 100% complete response rates after combination TACE–microwave ablation were confirmed by Tshihito et al,²³ albeit again for lesions <3 cm. Studies are lacking in TACE–microwave ablation combination

treatment for lesions >3 cm. There are many similarities between RFA and microwave ablation, including the type of energy (electromagnetic spectrum), temperatures reached, and ablation efficacy. Preliminary results suggest that microwave ablation may have some advantages over RFA. The reported advantages include larger coagulation volumes and less susceptibility to the “heat-sink” effect. Microwave ablation also results in more rapid development of lethal temperatures and has a decreased likelihood to cause tissue charring. Even without these advantages, it is reasonable to expect microwave ablation to at least mirror RFA as far as efficacy, effectiveness of combination therapy with TACE, and possible survival benefit to patients with intermediate-size liver tumors.

TACE – CRYOABLATION

At a median 3.5-year follow-up comparing combination TACE–cryoablation and cryoablation alone, Ke-Cheng et al found a recurrence rate of 11% and 23%, respectively ($p = 0.001$) (Fig. 4).²⁴ Though survival was no different at 1, 2, and 3 years, TACE–cryoablation combination did result in a 4- and 5-year survival benefit. The 4- and 5-year survival rates were 49% and 39% in the TACE–cryoablation group and 29% and 23%, respectively, in the cryoablation alone group ($p = 0.001$) (Fig. 5). Similarly, Clavien et al²⁵ reported an 87% 2.5-year survival rate after combination TACE–cryoablation in a group of patients with unresectable HCC. The above data confirm what has been shown for RFA repeatedly: that combination TACE and ablation treatment improves response rates, local tumor recurrence rates, and survival of patients with unresectable HCC. Again, one must question the utility of adding TACE to the treatment protocol of a patient with an HCC <3 cm. It does appear, however,

Figure 4 There is a 3.5-year local recurrence risk for unresectable hepatocellular carcinoma after cryoablation alone (mean tumor size 4.6 cm) versus transcatheter arterial chemoembolization– (TACE–) cryoablation (mean tumor size 6.3 cm). Despite the larger lesion size for the TACE–cryoablation group, local recurrence rates were lower at 3.5 years. This follows qualitative data on TACE–radiofrequency ablation treatments, and confirms the value of combination treatments for intermediate-size lesions.

Figure 5 Survival rate of patients with unresectable hepatocellular carcinoma (HCC) treated with a combination transcatheter arterial chemoembolization–cryoablation (gray) versus cryoablation alone (black). Although there is no statistically significant survival benefit for the first 3 years, a statistically significant chance for greater than 4- and 5-year survival can be seen in the combination treatment group, again supporting the value of combination treatments for intermediate-size HCC.

that for intermediate-size liver lesions, combination TACE–cryoablation does confer response and survival advantages.

TACE–OTHER

Other ablative methods are available to be used in combination with TACE, namely percutaneous ethanol injection (PEI), laser coagulation therapy (LCT), and high-intensity focused ultrasound (HIFU). There is indeed strong evidence that PEI in combination with TACE does improve response rates and survival for HCC patients. However, PEI individually shows significantly lower response rates than any of the thermal ablative techniques and requires more sessions. It has therefore fallen out of favor in the United States. LCT is mostly used in Europe and shows very good results, approaching those of other thermal ablative modalities. Finally, HIFU is a much newer modality and data are lacking, especially for combination treatments.

DISCUSSION

Despite recent technologic and pharmacologic advances in the treatment of HCC, including the development of drug-eluting beads and more effective systemic chemotherapy drugs, unresectable HCC remains a disease with extremely poor prognosis. Multiple studies have suggested that improved survival is strongly related to better tumor response to treatment. The objective of any treatment protocol should therefore be to achieve the maximum response possible. This has in turn propelled combination treatments to the forefront of research and clinical use, hoping that they will

Figure 6 Schematic of theoretical benefits of transcatheter arterial chemoembolization–radiofrequency ablation (TACE–RFA) versus RFA–TACE treatment. In the first row, RFA is offered first. After ablation, a peripheral hyperemic rim is present (arrow). During TACE, this increased local vascular supply to peripheral of target lesion improves the deposition of the TACE cocktail. In the second row, TACE results in a diminished regional blood flow to and around the target lesion, mitigating the “heat-sink” effect and resulting in a larger ablation volume.

improve tumor response rates and by extension patient survival. It is well known that TACE rarely results in complete tumor response. It does, however, treat entire lesions irrespective of size. On the other hand, ablative methods are considered curative options, but they are limited by lesion size. Therefore, their combination should reasonably be expected to improve lesion response. This has been born out in multiple studies, especially for RFA. Whether ablation should precede TACE or vice versa is a matter of debate. Supporters of the former claim that after ablation, the hyperemic ring around the tumor bolsters the effect of TACE. Supporters of the latter propose that the reduction in vascularity after TACE yields a larger ablation volume (Fig. 6).²⁴ Multiple trials are currently under way investigating such combination treatments, including TACE and systemic chemotherapy, drug-eluting beads and systemic chemotherapy, TACE and ablative therapies, and ablative therapies and systemic chemotherapies, among others. Despite the lack of prospective randomized studies and level 1 evidence, there is strong lower level evidence that suggests that combination ablative and intraarterial treatments improve both tumor response rates and survival in patients with intermediate-size lesions. The exact size range is not well defined, but certainly for the addition of TACE to be beneficial the lesion must be 3 cm or larger. The upper size limit for combination treatments to be more effective than monotherapy is not well defined. Patients with lesions up to 5 cm do appear to benefit from combination treatments, and it is likely patients with larger lesions may also benefit.

	Lesion Size	CR rate	Survival				
			1-year	2-Year	3-Year	4-Year	5-Year
TACE-RFA	< 3 cm	100%	Same as RFA	Same as RFA	Same as RFA	Same as RFA	NA
	3-5 cm	~ 100%	Improved	Improved	Improved	NA	NA
	> 5 cm	NA	NA	NA	NA	NA	NA
TACE – microwave	< 3 cm	100%	Same as microwave	NA	NA	NA	NA
	3-5 cm	~ 100%	NA	NA	NA	NA	NA
	> 5 cm	NA	NA	NA	NA	NA	NA
TACE – cryoablation	< 3 cm	100%	Same as cryoablation	Same as cryoablation	Same as cryoablation	Improved	Improved
	3-5 cm	~ 100%	Same as cryoablation	Same as cryoablation	Same as cryoablation	Improved	Improved
	> 5 cm	NA	Same as cryoablation	Same as cryoablation	Same as cryoablation	Improved	Improved

Figure 7 Summary of current data on radiologic response rates and survival benefit of combination therapies for unresectable HCC. Because lesions ≤ 3 cm respond very well to all ablation methods, it is instructive to categorize the response and survival benefit according to size. Universally, studies report 90 to 100% complete response (CR) rates for lesions ≤ 3 cm after ablation. Therefore, the addition of transcatheter arterial chemoembolization (TACE) is not expected to contribute significantly. This is apparent for both CR rates and survival rates, which are not affected by the addition of TACE to radiofrequency ablation (RFA). Notably, TACE alone is not expected to yield near a 100% response rate for lesions ≤ 3 cm, therefore patients with recurrence after TACE may still benefit from ablation. Despite a lack of long-term data regarding the efficacy and the survival benefit of TACE–microwave ablation, it is reasonable to assume that results should mirror those of RFA. Cryoablation shows an excellent response profile for small hepatocellular carcinoma (HCC). Combination TACE–cryoablation for unresectable HCC was reported to improve 4- and 5-survival over cryoablation or TACE alone. As a final note, it should be remembered that randomized prospective studies are lacking. The above data therefore is not generally viewed as evidence to implement a new standard of care. The decision to use single or combination treatments should be made on an individual basis. NA, not applicable.

CONCLUSION

In summary, there is strong evidence that for lesions <3 cm, the addition of TACE to ablative therapy does not improve response rates or survival. There is strong evidence, albeit not level 1, that for lesions 3 to 5 cm, combination treatments improve response rates, local tumor recurrence rates, and patient survival. There is weak evidence that combination therapy may improve response rates and survival for lesions >5 cm (Fig. 7). For such lesions, TACE should be the primary treatment with ablation added if there is a reasonable expectation of benefit, judged on an individual basis.

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