Transcatheter Arterial Chemoembolization Combined with Radiofrequency Ablation for the Treatment of Hepatocellular Carcinoma

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Key Words

Hepatocellular carcinoma · Radiofrequency ablation · Transcatheter arterial chemoembolization

Abstract

Radiofrequency ablation (RFA) has become an important treatment for hepatocellular carcinoma (HCC). Nowadays, RFA is generally recognized as an alternative treatment to partial hepatectomy for early HCC, especially for patients with impaired liver function and when liver transplantation is not indicated, although some authors consider that RFA can be used as a first-line treatment for early HCC. Transcatheter arterial chemoembolization (TACE) is most commonly classified as palliative rather than potentially curative; there is evidence that TACE prolongs survival in patients with well-compensated liver disease and intermediate-stage HCC. Alone, TACE and RFA have their limitations; in particular, neither can result in adequate control of medium or large HCC. Sequential application of TACE and RFA is, therefore, increasingly being used in the treatment of HCC in patients with well-compensated liver disease. In this study, we will introduce our experience of TACE combined with RFA in the treatment of HCC in a cancer center in China.

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The incidence of hepatocellular carcinoma (HCC) has increased dramatically worldwide in the past decade, making it currently the sixth most common cancer in the world and the third most frequent cause of cancer death [1]. Although more patients with HCC are being diagnosed at an earlier stage by surveillance using ultrasonography and fetoprotein levels [2–4], most HCCs are diagnosed at intermediate or advanced stages, and only 30% of patients benefit from curative therapies such as resection, liver transplantation or percutaneous ablation [5, 6]. Until now, no standard therapy has been established for treatment of HCC [7–10]. Transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are minimally invasive options that may individually or in combination achieve the pertinent balance in successful tumor eradication and maximal preservation of liver function. TACE can slow tumor progression and improves survival by combining the effect of targeted chemotherapy with ischemic necrosis by arterial embolization [11, 12]. Although TACE is most commonly classified as palliative rather than potentially curative, there is evidence that TACE prolongs survival in patients with well-compensated liver disease and intermediate-stage HCC [13–16]. RFA has become an important treatment for HCC [17]. RFA has emerged as an accepted ther-

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apy for early HCC because of its effectiveness and safety [18]. The optimum candidates for RFA are patients with HCC at an early stage (solitary tumor <5 cm in diameter or fewer than 3 nodules <3 cm in diameter). Nowadays, RFA is generally recognized as an alternative treatment to partial hepatectomy for early HCC, especially for patients with impaired liver function and when liver transplantation is not indicated, although some authors consider that RFA can be used as a first-line treatment for early HCC [10, 19, 20]. However, the likelihood of complete ablation using RFA declines rapidly as tumor diameter increases [21]. The complete response rate after RFA for HCC ≤ 2 cm is over 90%, but the local failure rate in individuals with HCC between 3.1 and 4 cm may be 24% with patients treated with RFA, and the likelihood of complete ablation rapidly declines beyond 4 cm [6]. Either TACE or RFA has its own limitations, in particular, neither can result in adequate control of medium or large HCC [6, 8–10, 13, 14]. Because blood flow promotes heat loss, and heat loss may reduce the effectiveness of RFA, a possible way to increase the ablation size of RFA thermal lesions would be to reduce or eliminate the heat loss that is mediated by tissue perfusion [21]. Blood flow to HCC lesions can be substantially reduced by the arterial embolization effect of TACE treatment. Moreover, TACE has a strong antitumor effect on HCC lesions. The synergy between TACE and RFA is well described [21, 22]. Occlusion of hepatic arterial flow by embolization reduces the cooling effect of hepatic blood flow on thermal coagulation. Furthermore, iodized oil and gelatin sponge particles used in TACE fill the peripheral portal vein around the tumor by going through multiple arteriportal communications [23, 24], thus reducing the portal venous flow. As a consequence, RFA can enable the creation of larger thermal lesions by RFA. The effect of chemotherapeutic anticancer agents on cancer cells enhances the effect of hyperthermia [25]. TACE, being a regional treatment, can target undetected satellite lesions outside of the zone of RFA-induced necrosis. Moreover, disruption of intratumoral septa, which usually happens after TACE, facilitates heat distribution within the tumor, and intratumoral septa and fibrosis are considered to hamper heat diffusion within the tumor [26]. Sequential application of TACE and RFA is, therefore, increasingly being used in the treatment of HCC in patients with well-compensated liver disease.

Recently, some studies have compared the efficacy of combined TACE and RFA with RFA alone for the treatment of HCC. A recently published randomized controlled trial by Shibata et al. [27] demonstrated a survival

equality for combined TACE and RFA ($n = 46$) compared with RFA alone ($n = 43$) in patients with Child's A or B cirrhosis and resectable HCC with ≤ 3 nodules smaller than 3 cm. In this study, after treatment, the 1-, 2-, 3- and 4-year rates of local tumor progression, overall survival, local progression-free survival and recurrence-free survival were as follows: local tumor progression 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 ($p = 0.797$). Overall 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 RFA group ($p = 0.515$). Local progression-free survival rates were 84.6, 81.1, 69.7 and 55.8%, respectively, in the combined treatment group and 88.4, 74.1, 74.1 and 61.7%, respectively, in the RFA group ($p = 0.934$). Event-free survival rates were 71.3, 59.9, 48.8 and 36.6%, respectively, in the combined treatment group and 74.3, 52.4, 29.7 and 29.7%, respectively, in the RFA group ($p = 0.365$). In light of this study, the authors considered that combined RFA plus TACE and RFA alone have equivalent effectiveness for the treatment of small (≤ 3 cm) HCCs, and they thought the combination treatment may not be necessary. In the study, both treatment groups had low rates of major complications (2.2–2.3%) and it was stated that treatment of HCC by combined TACE and RFA was safe. Morimoto et al. [28] reported the midterm outcomes of a randomized controlled trial comparing the efficacy of TACE combined with RFA with RFA alone for the treatment of intermediate-sized HCC. In the study, the authors randomly assigned 37 patients with solitary HCCs (diameter 3.1–5.0 cm in the greatest dimension) to 2 groups: the TACE combined with RFA (TACE-RFA) group, and the RFA group. The results showed that technical success was achieved after 1.4 ± 0.5 RFA sessions in the RFA group and after 1.1 ± 0.2 RFA sessions in the TACE-RFA group ($p < 0.01$). The mean diameters of the longer and shorter axes of the RFA-induced ablated areas were 50 ± 8.0 and 41 ± 7.1 mm, respectively, in the RFA group and 58 ± 13.2 and 50 ± 11.3 mm, respectively, in the TACE-RFA group; the mean diameters of the shorter axes were significantly different ($p = 0.012$). The rates of local tumor progression at the end of the third year in the RFA and TACE-RFA groups were 39 and 6%, respectively ($p = 0.012$). The 3-year survival rates of the patients in the RFA and TACE-RFA groups were 80 and 93%, respectively ($p = 0.369$). The authors reported that TACE prior to RFA expanded the short axis of the ablated area and resulted in a more spherical ablated area. They postulated that a spherical ablated area was more effective than a

nonspherical ablated area in ensuring local tumor control because a spherical ablated area was more likely to completely cover the target tumor. TACE-RFA was also a safe treatment in this study. The result showed that there were no severe side effects during the procedures in the study; however, 6 patients (5 patients of the RFA group and 1 patient of the TACE-RFA group) experienced grade 1–2 pain lasting several hours. Major complications were not observed in the patients of the 2 groups. Minor complications, including asymptomatic right pleural effusion, were noted within 3 days of the procedures in 2 patients of the RFA group and 1 patient of the TACE-RFA group (RFA group vs. TACE-RFA group, $p = 0.515$). Therefore, the role of TACE combined with RFA in the treatment of HCC needs further study.

Recently, some authors have used meta-analysis to verify the role of TACE combined with RFA in the treatment of HCC. In the work of Yan et al. [29], 19 studies (including 4 randomized control trials) were included into the meta-analysis. Meta-analyses showed that the combination of RFA and TACE was associated with higher survival rates (1-year OR = 2.14, 95% CI 1.57–2.91, $p = 0.001$; 3-year OR = 1.98, 95% CI 1.28–3.07, $p = 0.001$; 5-year OR = 2.70, 95% CI 1.42–5.14, $p = 0.003$). They postulate that the combination of TACE with RFA can improve the overall survival rate and provide better prognosis for patients with HCC, but more randomized controlled trials using large sample size are needed to provide sufficient evidence. In another meta-analysis study, Wang et al. [30] reported that there was no survival benefit from TACE combined with RFA in treating small HCC (≤ 3 cm) patients as compared with that of RFA alone. The advantages of TACE-RFA may be as follows: TACE can block the hepatic arterial flow and contribute to the decrease in heat-sink effects and the increase in the necrotic area induced by RFA, and the effect of anticancer agents on cancer cells may be enhanced by the hyperthermia. However, these advantages do not seem to have any indication according to Wang et al.'s [29] meta-analysis for small HCC. The reason for this may be that RFA has already achieved complete necrosis in $>90\%$ in treating small HCC nodules [31], suggesting that adding TACE to RFA seems to be redundant in producing an assessed outcome. Schwartz and Weintraub [32] considered that the clearest role for the combination of TACE and RFA is to increase the likelihood of complete destruction of HCC nodules that are in the range of 3–5 cm. They also say that patients selected for combined TACE and RFA should have well-compensated cirrhosis, and the rationale for using combined therapy is strongest for patients with uninodular HCC.

We agree with that idea. Recently, a randomized controlled trial published by us demonstrated that the survival benefit for combined TACE and RFA ($n = 94$) was comparable with RFA alone ($n = 95$) in patients with Child's A or B cirrhosis and resectable HCC with ≤ 3 nodules smaller than 7 cm [33]. In our study, after treatment, the 1-, 3- and 4-year overall survival rates for the TACE-RFA group and the RFA group were 92.6, 66.6 and 61.8%, and 85.3, 59 and 45.0%, respectively. The corresponding recurrence-free survival rates were 79.4, 60.6 and 54.8%, and 66.7, 44.2 and 38.9%, respectively. Patients in the TACE-RFA group had better overall survival and recurrence-free survival than the RFA group ($p = 0.002$ and 0.009 , respectively). After multivariate analysis, treatment allocation, tumor size and tumor number were significant prognostic factors for overall survival, while treatment allocation and tumor number were significant prognostic factors for recurrence-free survival. There were no treatment-related deaths in this study. In light of this study, the role of combined TACE and RFA warrants careful consideration. The study provides evidence that altering the tumor microenvironment and supporting vasculature may help improve the efficacy of locoregional therapy in HCC. We therefore think that, in the future, the standard of care for HCC treatable with RFA should shift toward the combination treatment. We know that RFA has already begun to challenge the status of resection as the optimum treatment for HCC ≤ 2 cm; combined RFA and TACE will certainly broaden this challenge. In the future, further logical studies will be to investigate the potential benefit offered by complementary treatment modalities, such as targeted agents in combination with TACE-RFA [11, 12].

Disclosure Statement

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