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Int. J Cell Biol. Physiol. 2018: 1 (1-2), 19-23

Short Article

RFA-based combinational treatment against hepatocellular carcinoma

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(Received Dec 2, 2018; Accepted December 26, 2018)

Hepatocellular carcinoma (HCC) is the third most leading cause of cancer related death worldwide, according international agency for research on cancer, HCC also could account for the fifth most common cancer worldwide. [1] Due to that HCC is often detected in late stage in many cases, there is no clear symptom at early stage, and complicated tumor status including number, size, portal invasive and extrahepatic disease, most of patients with HCC are not suitable for liver resection or liver transplantation. Imaging-guided radiofrequency ablation (RFA) is alternative treatment as a curative method destructing HCC in patients who are not able to take surgery resection [2].

In clinic, the implications of RFA mainly include primary treatment for tumor lesions their diameter is less than 3 cm, unresectable small HCC, recurrent small HCC, bridging therapy before liver transplantation Advantage over surgery resection has been shown owing to reduced morbidity by ablating a relatively small portion of liver and extended life expectancy of many patients. [3] RFA has been attracting attentions as the first line option in HCC treatment along with improvement of modern medical technique, playing increasing role not only for small tumors but also for tumors their diameters are more than 3 cm in HCC treatment. However, in consideration of clinical complication and recurrence, RFA has limitations. It only can produce best results as a 5 years survival of 40-70% if the patients with single tumor and diameter are less than 2 cm. There will be a complete response in 80% tumors if tumors are less than 3 cm, and in 50% if tumors are 3-5 cm with a 70-81% new tumor recurrence.

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Given that, substantial investigations have been performed to explore the therapeutically improved new strategy based on utility of RFA for HCC treatment. Several RFA-based therapeutic strategies against HCC will be discussed here.

People have found that one of main factors which induce an uncomplete tumor response to RFA is inability to produce adequate tumor cell destruction in ablation. [4] Obviously, it may explain why RFA provides better prognosis in small tumor lesions. In RFA operation, heat-sink effect of tumor blood flow plays an important role to weaken RFA induced thermal injury in tumors through reducing electromagnetic energy deposition, because the blood flow will bring heat away from tumor site. Despite the methods were used to decease tumor blood flow, such as Pringle maneuver and chemoembolization, [5, 6] but all of them require invasive procedures which oppose the intent of RFA as minimally invasive performance. Thus, RFA in combination with administration of antiangiogenic pharmaceutical agent, sorafenib, has been performed in a study using animal subcutaneous tumor model. [7] They treated tumor bearing mice with sorafenib in different doses before RFA was performed. Data shown the treatment of sorofenib significantly increased RFA induced coagulation necrosis diameter on tumor site in dose dependent manner. Likewise, significant reduction of MVD (microvascular density) was observed in response to sorafenib administration. It should be noted that sorafenib has been shown anti-tumor activity as multiple targets receptor tyrosine kinase inhibitor and approved as anti-cancer drug in patients with HCC by FDA. In this study, sorafenib was demonstrated its synergistic effect with RF ablation induced tumor necrosis through its vascular endothelial growth factor (VEGF) inhibitor activity. Combination of RFA physically induced tumor destruction and anti-tumor activity of sorafenib may exert a much better prognosis in patients with HCC. Actually, the same group they have tried to use arsenic trioxide to inhibit tumor blood flow in their previous study. Data indicate arsenic trioxide administration represents a transient effect reducing tumor blood flow during RFA, thus enabling a larger coagulation necrosis zone in tumor [8]. But sorafenib may be a better option to pursue application in clinic.

In order to optimize the clinical benefit of RFA, one study compared combined TACE (transarterial chemoembolization) and RFA versus RFA alone in a prospective randomized trial [9]. 189 patients with HCC less than 7 cm were involved in this trial.

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Patients were randomly assigned to receive RFA combined with TACE or RFA alone, between which, overall survival, recurrence free survival and adverse effects were compared. All data together demonstrated combinational treatment was superior to RFA alone. RFA has been supported as a first line treatment option for small HCC from extensive experience worldwide. Contrast to RFA, TACE has been recognized as standard of care for patients with intermediate-stage tumor with multi-nodular lesions but without vascular invasion. All procedures of TACE result in ischemic tumor necrosis by occluding hepatic arterioles where HCC derives its blood supply almost entirely from [10]. Theoretically, combination of RFA and TACE can overcome limitations of each of them which was strongly supported by this study.

As a potential curative treatment for cancer, anti-tumor immunotherapy has been a hot field in cancer study for a relative long time [11-13], and many promising immunotherapy-based strategies against HCC have been establised. Check point blockade has been approved by FDA to be used clinically for anti-cancer treatment in several different types of tumor that is a milestone in development of cancer treatment. In a retrospective case-contrasted study, tumor infiltrating T cell and tumoral PD-L1 expression were analyzed in patients with colorectal cancer liver metastasis with or without RFA before liver tumor resection Investigator also evaluated anti-tumor effect in combination of RFA and PD-1 blockade in mouse tumor model. They found RFA treatment in clinic increased tumor T cell infiltration, meanwhile the PD-L1 was upregulated in tumor. In their experimental study, RFA in combination with anti-PD-1 antibodies significantly enhanced T cell immune response, thus exert a stronger anti-tumor efficacy and produced prolonged survival in HCC tumor mice model [14].

Besides checkpoint blockade, some other anti-tumor immunotherapy strategies have been studied in combination with RFA for improved therapeutic efficacy. In a clinical study, 62 patients with HCC were treated with radical RFA alone or RFA combined with cellular immunotherapy (CIT). For CIT, the autologous mononuclear cells were collected from peripheral blood, then induced into natural killer cell and cytotoxic T cells which were identified and infused intravenously to patients for three or six courses. All patients were monitored by CT / MRI to track HCC recurrence every 3 months after RFA. Progression free survival (PFS), liver function, viral load and adverse effects also were

examined. The results demonstrate - combinational treatment produced a better PFS [15]. In a expermental study, investigator treated tumor bearing mice with ECI301, an active variant of CC chemokine ligands 3, after RFA treatment. Administration of ECI301 augmented RFA induced anti-tumor effect by increasing T cell infiltration. [16]

Despite increasing data in both clinic and experimental study about how to improve RFA efficacy by combination with anti-tumor chemotherapy, radiotherapy, targeted small molecules and immunotherapy, there is no RFA–based combinational treatment standard for HCC applicable in clinic currently. More data from clinical trial will be expected.

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