Does Radiofrequency Ablation Stimulate a Higher Malignant Potential of Hepatocellular Carcinoma?

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Radiofrequency ablation (RFA) is an established treatment for BCLC 0-A hepatocellular carcinoma (HCC) associated with minimal invasiveness and a high rate of curability [1]. Recent large scale, long-term follow-up study from Korea demonstrated the 5 and 10 year overall survival rates in 1,305 patients with early HCC treated with RFA to be 59.7 % and 32.3 % respectively [2].

However, to date, it remains under debate which is superior, surgical resection or RFA, with respect to the overall survival and recurrence rates in patients with early HCC [3,4]. A major drawback of RFA is the high rate of tumor recurrence after the therapeutic procedure, which affects the patient survival and is the main reason why RFA is considered to be inferior to surgical resection in cases of resectable lesions [5]. In the aforementioned study from Korea, Kim et al. demonstrated the 5 and 10 year cumulative local tumor recurrence rates to be 27.0 % and 36.9 % respectively, with 5 and 10 year cumulative intrahepatic distant and extrahepatic recurrence rates of 73.1 %/ 88.5 % and 19.1 %/ 38.2 % respectively [2].

The presence of an insufficiently ablated margin, in addition to a large tumor size, is a major risk factor for tumor recurrence after RFA. Lee et al. reported that an insufficiently ablated margin is an independent factor predicting early diffuse recurrence (three or more new lesions of intrahepatic recurrence within one year after the initial RFA procedure) [6]. Some investigators have reported early and serious recurrence of HCC after RFA, leading to poor survival outcomes [7,8]. These reports suggest the phenotypic and functional alteration of HCC cells after RFA.

More recently, in vol. 58 issue 5 of Hepatology, Yoshida et al. demonstrated that sublethal heat treatment of HCC cells endows these cells with a higher proliferative and carcinogenic potential in both *in vitro* and *in vivo* studies [9]. The authors exposed three human HCC cell lines (HEPG2, HuH7 and HEP3B) to 37°C, 45°C, 50°C and 55°C for 10 minutes, simulating the marginal zone of RFA treatment. They subsequently analyzed the degree of cell proliferation, parameters of the epithelial-mesenchymal transition (EMT) and the level of activation of mitogen-activated protein kinases 5-12 days after treatment. Although all HCC

cells died following exposure to a temperature of 55°C, 65-85 % of the HCC cells survived exposure to temperature of 48-50°C, thus exhibiting distinct morphological changes, such as the appearance of spindle-like cells, and expressing the progenitor marker, CD133, the cholangiocyte markers, CK7 and CK19, and the EMT-related transcription factor, Snail, on day 5 after heat exposure. The HCC cells exposed to 50°C showed enhanced proliferation and activation of Src homology and collagen (Shc), a central player in malignant transformation. Moreover, in order to evaluate how far heat treatment can induce more aggressive (EMT-like) tumor growth *in vivo*, the authors transplanted heat-exposed HEPG2 cells into nude mice. The heat-exposed HEPG2 cells implanted into the nude mice induced the growth of significantly larger, more aggressive tumors than the untreated cells, as well as enhanced proliferation and the upregulation of various markers of the EMT. The authors concluded that insufficient or sublethal heat treatment stimulates a higher malignant potential by skewing HCC cells toward the EMT and transforming them into a progenitor-like, highly proliferative cellular phenotype both *in vitro* and *in vivo*.

The above study supports the presence of early and serious recurrence leading to unfavorable outcomes after RFA [6-8] and stresses the need to apply sufficiently high temperatures and obtain wide therapeutic margins. Clinicians should therefore recognize the possibility of malignant transformation of HCC cells subject to heat treatment, such as RFA. In such cases, the need for additional treatment, including surgical resection and/or TACE, should be carefully taken into consideration.

Conflict of Interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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