REDELVE INTERNATIONAL PUBLICATIONS

Journal of Surgery Open Access
Volume 2019, Issue 01
Mini Review: RD-SUR-10004

A Comprehensive Impact on Systemic Antitumor Immunity by Radiofrequency Ablation

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Citation: *Xiaoqiang Qi, Ming Yang and Sathisha Upparahalli Venkateshaiah (2019) A Comprehensive Impact on Systemic Antitumor Immunity by Radiofrequency Ablation. Journal of Surgery Open Access: RD-SUR-10004.*

Received Date: *26 January 2019;* ***Acceptance Date:*** *5 February 2019;* ***Published Date:*** *8 February 2019*

Mini Review

Radiofrequency ablation (RFA) has been become the first line option in clinical treatment for solid tumor such as liver cancer (HCC), renal cancer, liver metastasis of colorectal cancer and so on. In principle, RFA locally destroys tumor by coagulation necrosis through electromagnetic energy deposition. RFA has been shown having its unique advantages over surgical resection due to its minimally invasive operation. With the development and application of imaging technique, image guided RFA is capable of fully tumor destruction without any incision, bleeding. With the extensive use of RFA in clinical practice, the more findings in RFA induced anti-tumor immune responses have emerged. It reveals RFA is not only a local tumor destruction [1].

As early as 2003, a case report descripted a spontaneous regression of pulmonary metastasis after RFA treatment on primary tumor of renal cell carcinoma [2]. It shown pulmonary metastasis was completely disappeared in the follow-up of CT/MRI check at 10 months with no enhancement of primary renal cancer after RFA. People believed a systemic antitumor immune response was induced by RFA which could result from tumor specific antigen release that augments host immune response. So, the following question was raising, what's the mechanism underlying effect of promotion in antitumor immunity by RFA?

In a clinical investigation, eight patients were treated with RFA or PEI (Percutaneous Ethanol Injection), PEI is another local treatment method for HCC, and serially analyzed for 4 weeks. The phenotypes and function of dendritic cells (DCs) from each patient were tested. After a local tumor destruction by either RFA or PEI, there were an increased serum level of TNFα and IL-1β which indicated the local therapy on HCC could lead to a systemic immune response in the host body. Also, the myeloid DCs were found transiently activated after operation, but not plasmocytoid DCs in this investigation [3]. It is reasonable to have a hypothesis that local tumor cell injury may result in release of endogenous tumor antigen and other activating substances that can function as nature adjuvants to activate myeloid dendritic cells.

The maturation of DCs is supposed to activate tumor antigen specific effecter CD8+ T cell, and the local release of endogenous activating substance could attract more effecter CD8+ T cells to tumor sites. So antitumor effecter CD8+ T cells play a critical role in RFA induced immunogenicity [4]. In another clinical study, HCC-associated antigens specific T cell

responses after RFA on HCC patients were tested. Peripheral blood mononuclear cells from 20 HCC patients were stimulated with autologous HCC-derived protein lysates to get IFNγ production. The data show that RFA caused a significant increase in circulating tumor-specific T cell, and T-cell responses to recall antigens (function of memory T-cell) were also significantly augmented by RFA [5].

In the same study, the activation and cytotoxic markers of circulating T cell and nature killer (NK) cell were found having an increased expression which implied not only CD8 T cell, but NK cells may be involved in RFA induced boost in anti-tumor immunity. One published report demonstrated that RFA on HCC stimulates autologous NK-cell response [6]. 37 patients with HCC undergoing RFA were included in this investigation to characterize phenotype and function of NK cells. Both of frequency and absolute number of NK cell were increased after RFA, activation related markers were upregulated, meanwhile the inhibitory markers were reduced in phenotype which positively correlated with increased function of NK cells at 4 weeks after RFA treatment. More important finding is the recurrence-free survival of patients was observed to have a positive correlation with functionally activated phenotype of NK cells which suggested the RFA induced NK cell response may play role in suppression of local tumor recurrence and distant metastasis in HCC patients undergoing RFA treatment.

The local tumor cell destruction by RFA will release lots of endogenous tumor associated antigen, furthermore, within periablational zone the local collagen and fibrosis deposition and various systemic activating factors such as IL-6, heat shock proteins, hyperthermia will be induced by RFA caused tumor injury. All these RFA induced tumor necrosis and inflammatory periablational zone remain in situ after RFA operation, people have explored what's the subsequent impact of these remnants in situ to patients undergoing RFA in both two opposite directions, not only enhanced tumor antigen specific immune response [1,3,5,7-9], but also oncogenesis which may be associated with liver regeneration in wound healing process after a local RFA [10,11]. One mission raised out of these contrary effects by RFA, how to develop a combinational treatment strategy, treating HCC by RFA combined with other adjuvants to take full advantage of RFA released antitumor immunogenic factors, meanwhile inhibit effect of those adverse factors. Our lab is devoted to decoding this complex with hope of development of new combinational strategy improving RFA efficacy against HCC in a clinical relevant orthotopic murine model [12-15].

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