Thermal ablation in cancer (Review)

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Abstract. Radiofrequency ablation (RFA) and cryoablation are alternative forms of therapy used widely in various pathological states, including treatment of carcinogenesis. The reason is that ablation techniques have ability of modulating the immune system. Furthermore, recent studies have applied this form of therapy on tumor microenvironment and in the systematic circulation. Moreover, RFA and cryoablation result in an inflammatory immune response along with tissue disruption. Evidence has demonstrated that these procedures affect carcinogenesis by causing a significant local inflammatory response leading to an immunogenic gene signature. The present review enlightens the current view of these techniques in cancer.

Contents

1. Introduction

Interventional procedures involving exposure to extreme temperatures to cause local tissue damage are termed as thermal ablation (1). The two most commonly used procedures that comprise thermal ablation, are radiofrequency ablation (RFA) and cryoablation. The two procedures involve the introduction of a metal probe using ultrasound or computed tomography (CT) guidance as a visual aid. Small tumors are usually destroyed by exposing them to two different temperature extremes, high burning temperature via RFA and freezing tissue cold temperature via cryoablation.

In terms of local treatment strategies, cryoablation is an attractive treatment modality as it is safe and effective in the treatment of kidney, liver, bone, lung, adrenal and soft tissue masses (2,3). Furthermore, it is palliative in nature as the freezing procedure causes a local analgesic effect. Cost effectiveness is another positive aspect of cryoablation. Additionally, cryosurgery is another ablation method showing progress in prostate and breast cancer subjects and has thus become a widely applied technique in research for both immunologists and oncologists (2,3).

2. Cryoablation and cancer

Cryoablation has been reported to induce microvascular thrombosis, membrane disruption, solution effects, ice crystallization and organelle disruption in cancer cells (4). These differentially induced processes affect cells variably and eventually result in apoptosis or even necrotic cell death (5). Reiter *et al* observed that cryotherapy was more effective in exerting an antitumor effect by virtue of cell necrosis as compared to ultraviolet (UV)-induced apoptosis in bone marrow-derived murine macrophage (6). Sauter *et al* evidenced the specificity of cryotherapy by inducing necrosis on immature dendritic cells (DCs) as they have ability to induce apoptosis and necrosis (7).

Previous studies have focused on the nature of cryotherapy-induced immune effects, i.e., immunosuppressive or immune-stimulatory. The 'danger' theory suggested the immune system is capable of recognizing any cell injury as a threat, thereby inducing responses. This is termed immune-stimulatory (8). Similarly, cryotherapy-induced necrosis is immune-stimulatory in nature as it leads to the denaturing of proteins or cell wall breakdown. Immune stimulation during cryotherapy is visible in the form of high mobility group box 1 (HMGB1) inflammatory factor, uric acid, and heat shock proteins (HSPs), including hsp70 and hsp90 (9). On the other hand, apoptosis is immune suppressive in nature and unable to release HMGB1 (10). Scheffer *et al* studied protective attributes of the two processes and observed that apoptotic cells induced significant protection and prolonged survival, while necrotic cell vaccine provided little protection (11). Conversely, Kotera *et al* found pulsing DCs with apoptotic cells produced

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by UVB exposure showed immune-stimulatory effects (12). Gamrekelashvili *et al* used ganciclovir to induce tumor cell apoptosis and a vascular targeting drug, ZD6126, to process necrotic tumor cells, thereby observing both immune-stimulatory as well as immune-suppressive effects (13). Feng *et al* also observed both these effects in leukemic cells (14). Therefore, the induction of necrotic and apoptotic cells is important in the generation of an immune-reactive or immunosuppressive response and cryosurgery is an important contributor to the management of carcinogenesis.

3. Surgical diathermy

Kolicher for the first time evidenced the efficacy of surgical diathermy during cancer in 1910 (15). The key player in this form of therapy was observed to be the reticuloendothelial system. In surgical diathermy, RFA is often utilized for therapeutic exposures. McGahan *et al* demonstrated the local effects of RFA via ultrasound including necrosis, hemorrhage and congestion in swine models (16). RFA was reported to cause statistically significant infiltration of T cells in a hepatoma model in rabbits (17). Additionally, in the combination approach, RFA together with CTLA4 was reported to be more effective against tumor and proved successful in the enhancement of survival (18).

4. RFA and its associated effects

RFA resulted in T-cell response together with the infiltration of DCs within tumors in a murine urothelial carcinoma model (19). In humans, RFA has been reported to be effective in metastatic liver tumors during hepatocellular carcinoma (HCC) (20). In an additional study, RFA promoted the release of interferon (IFN)-γ following the procedure (21). In another study, in 20 patients with localized HCC unfit for liver transplantation or surgical resection, RFA proved beneficial by promoting the frequency of circulation of IFN-γ-positive cells (22). Zerbini *et al* showed that RFA is also capable of inducing maturation of antigen-presenting cells (APCs) capable of producing specific T cells for HCC (23).

5. Cryosurgery in cancer

The approach of cryosurgery has also been reported to have an immune-stimulatory and immunosuppressive nature (24). Myers *et al* used mouse models for fibrosarcoma and mammary tumors to observe the effectiveness of cryosurgery (25). Using a rat model, Blackwood and Cooper found that animals who received cryoablation for myosarcoma and carcinosarcoma cell line-derived tumors were protected against intraperitoneal implantation (26). Neel *et al* also compared surgical approach and cryoablation in mice with virally-induced mammary adenocarcinoma or chemically-induced sarcoma. The results of that study showed that cryoablation was more efficient in improving survival time after tumor rechallenge (27).

6. Mechanism behind cryosurgery/RFA

The *in vivo* melanoma mouse model was utilized to determine mechanisms underlying cryosurgery, RFA and tumor vaccination. RFA and cryosurgery appeared to produce an *in situ* depot of tumor antigen and debris. These approaches have been observed to cause an increase in immature DCs within tumor draining lymph nodes that ultimately cause tumor invasion. Furthermore, as discussed earlier, the combination therapy was more beneficial and effective through the addition of anti-CTLA4 to any thermal ablation approach, whether. cryosurgery or RFA (18). It has also been suggested in the literature that these approaches result in an increased ratio of effector CD8 T cells compared to T-regulatory cells, thereby resulting in a systemic specific immunity.

7. Conclusion

Based on the above literature it can be concluded that thermal ablation procedures affect carcinogenesis by causing a significant local inflammatory response leading to an immunogenic gene signature. However, additional studies are required to clinically confirm the outcomes and to make it a gold standard therapy for the management of cancer patients.

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