Laparoscopic, Endoscopic, and Robotic Surgery xxx (2018) 1–7

Contents lists available at ScienceDirect

Laparoscopic, Endoscopic, and Robotic Surgery

journal homepage: www.keaipublishing.com/en/journals/laparoscopic-endoscopic-and-robotic-surgery

Harnessing macrophages in thermal and non-thermal ablative therapies for urologic cancers – Potential for immunotherapy

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ARTICLE INFO

Article history:
Received 15 November 2017
Received in revised form
17 January 2018
Accepted 25 January 2018
Available online xxx

1. The promise of macrophage directed therapy

Prostate and bladder cancers are one of the cancers occurring worldwide.[1] Developments in modern imaging has led to a rapid growth in the use of thermal and non-thermal based minimally invasive interventional therapies for the treatment of various urological cancers. Enhancements in these image-guided treatment modalities have made it more and more easier to target and destroy tumors. The currently available thermal ablative modalities include cryotherapy, high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA) and laser therapy. Non-thermal techniques include photodynamic therapy (PDT), irreversible electroporation (IRE) and radiotherapy. While conventional surgery aims to completely remove a solid tumor and sometimes local lymphatic drainage, ablation therapies cause destruction of cancer cells and leave antigenic material *in situ* which can prime a potential local and systemic immune response.

Emerging evidence shows that the immune system plays a vital role in the defence against cancer[2,3] opening new therapeutic approaches. For example, Matsumoto et al. recently showed that tumor-specific immune response can be evoked independently of general inflammatory reaction by stimulation of toll-like receptor 3 pathway in antigen presenting dendritic cells.[4] Furthermore, new antigens and oncoproteins expressed in cancer cells as they gain functions to invade and metastasise might be recognized by immune cells.[5] Ablation therapies cause cancer cell death via a combination of necrosis and apoptosis.[6] Antigenic material along with 'danger signals' like alarmins, DNA, RNA, and heat shock proteins from cancer cells are released and these mediators are then picked up by the surrounding lymphatic system potentially leading to an anticancer immune response.[7,8] However, ablation therapies have also been demonstrated to lead to an immunosuppressive effect mainly due to the activation of regulatory T cells (Tregs).[9] Tumor associated macrophages or M2 phenotype are now known to mediate this immunosuppressive pro-tumorigenic effect.[10] Alteration of macrophage differentiation may enhance tumor destruction of ablative therapy. This report aims to highlight the possibility of harnessing macrophages that can be directed towards destruction of tumor cells and the future potential of a combination of ablative modalities and immunotherapy.

2. Thermal ablative techniques

Thermal ablative modalities use either cold temperature as in cryotherapy or heat as in HIFU or RFA.

2.1. Cryotherapy

Cryotherapy utilizes extremely cold temperature to destroy tumor tissue. It turns the tumor into an ice ball resulting in cell death by cell membrane destruction and microvascular thrombosis. Cryoprobes are placed through transperineal route to ablate prostate cancer. Bladder cancer can be approached by transvesical route. Yantorno et al.[11] first demonstrated the immunomodulatory effect of cryotherapy in 1966 and coined the term 'cryo-immunology'. The term 'cryoimmunotherapy' was coined by Ablin et al.[12] as he

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https://doi.org/10.1016/j.lers.2018.01.001

Please cite this article in press as: Arthanareeswaran V-K-A, et al., Harnessing macrophages in thermal and non-thermal ablative therapies for urologic cancers – Potential for immunotherapy, Laparoscopic, Endoscopic, and Robotic Surgery (2018), https://doi.org/10.1016/j.lers.2018.01.001

observed a decrease in metastatic burden in prostate cancer patients following cryo-ablation. A nadir temperature averaging −40 °C is recognized as being more destructive than slow freezing.[13] This results in coagulative necrosis of the tissue subjected to high-rate freezing ensuing an acute phase response with leukocyte infiltration. However, tissue in the peripheral rim of the iceball, which is subjected to a lower freezing rate, undergoes cell destruction by apoptosis. This creates a zone of immune suppression,[14] which might explain why in some studies where an immunosuppressive effect was observed following cryotherapy.[15]

2.2. HIFU

HIFU uses the principle of a convex lens,[16] where, similar to light waves, sound waves are focused to create a central point of intense heat, to produce highly focused ultrasound waves using a transrectal spherical transducer resulting in thermal ablation of desired prostate tumor tissue. There have been ten studies on focal HIFU in prostate cancer that treated between 20 and 111 patients with 12–38 months of follow-up.[17] Post-treatment biopsy proven recurrence rates ranged between 11% at 6 months to 26.5% at 12 months of follow-up with acceptable potency and excellent continence rates.[18,19]

Temperatures up to 75 °C are achieved causing coagulative tissue necrosis. Cavitation effects occur in the treatment zone as a result of shear waves interacting with water to create microbubbles of gas, a phenomenon referred to as acoustic cavitation. These bubbles expand and collapse, leading to mechanical tissue destruction. In addition, it may also damage vasculature, leading to ischaemia and necrosis. As in cryotherapy, coagulative necrosis of treated tissue leads to an acute phase reaction. Hu et al. documented the release of danger signals like heat shock proteins (HSP) and Adenosine triphosphate (ATP) following HIFU therapy and showed upregulation of co-stimulatory molecules and enhanced dendritic cell (DC) activation.[20]

2.3. Focal laser ablation

Focal laser ablation Also referred to as laser interstitial thermotherapy, is a thermo-ablation technique which utilizes high-energy laser light to generate coagulation through rapid heating of targeted tissue. Energy is delivered to the prostate by laser fibres transperineally inserted through needles. The thermal effects produced by the laser energy spread from the absorption zone and lead to an increased temperature in the surrounding tissue. Coagulation necrosis occurs at the region of ablation.[21]

2.4. Radiofrequency ablation

Radiofrequency ablation (RFA) harnesses an alternating radiofrequency current to generate heat. As in HIFU and FLA, heat is generated to destroy tumor tissue. Renal RFA leads to necrosis and triggers apoptotic pathways as shown in a pig animal model[22] and induce systemic immune response and a significant tumor regression following re-challenge.[23]

3. Non-thermal ablative techniques

3.1. Photodynamic therapy

Photodynamic therapy is based on the interaction between light brought by a transperineally/transurethrally inserted laser fibre, a photosensitive agent (PS) and oxygen present in tissues. The absorption of a luminescent photon by the PS leads to a chain reaction resulting in achievement of a “triplet state” thereby inducing the production of ROS (reactive oxygen species), especially of singlet oxygen, and release antioxidant enzymes. This singlet oxygen can directly kill tumor cells by the induction of necrosis and/or apoptosis, can cause destruction of tumor vasculature, and produces an acute inflammatory response that attracts leukocytes such as macrophages and neutrophils. High PDT dose favours necrosis, as it disrupts enzymes necessary for apoptosis, inciting a cell-mediated response. An indirect effect results from damage to blood vessel endothelium and platelet adhesion, resulting in vascular occlusion and ischaemia. An adverse effect of high dose PDT in bladder cancer is that it may cause fibrosis and shrinkage of adjacent normal bladder tissues. Evans et al.[24] first described the stimulation of cytokine (TNF) release by macrophages following PDT. Sub lethal doses of PDT have also been shown to cause macrophage activation. Chen et al.[25] demonstrated that PDT may induce tumor-specific antibodies resulting in metastasis regression and resistance to tumor re-challenge. The study was done on a rat model with metastatic mammary cancer and was carried out with an immunoadjuvant linked to the photosensitizer. The mechanism of action provided useful information on how to optimise conditions for an immune response to be elicited.

3.2. Radiotherapy

Radiotherapy involves the use of ionising radiation to damage cellular DNA and disrupt the cell cycle, either through direct ionisation or the generation of free radicals. Although mechanism of tumor destruction has long been attributed to its direct effect on tumor cells, additionally an effective immune response can be triggered. Radiation-induced cytokine release, expression of damage-related molecular patterns in irradiated tumor cells and bystander effects may activate immune cells supporting tumor elimination.[26] Enhancing or restoring appropriate immune response by ionising radiation may be a promising approach. Depending on radiation dose both, pro-inflammatory anti-tumor immunity (high dose) as well as anti-inflammatory effects (low-dose) can result.[27] The combination of radiation with immunomodulatory substances such as 2-deoxy-D-glucose, which has been suggested to contribute to the successful tumor eradication by the polarization of macrophages towards M1 phenotype may also be considered[28]

Ionizing radiation has been described to release the high-mobility-group protein B1 (HMGB1) from cancer cells, which acts as a danger signal.[29] Toll-like receptor 4 detects HMGB1, and a study by Apetoh et al. demonstrated that subjects with a loss-of function allele for this receptor have higher relapse rates following radiotherapy.[30] Furthermore, Ionizing radiation may lead to translocation of a protein known as calcireticulin from the endoplasmic reticulum to the cell surface, which leads to antigen release and subsequent immune response.[31] However, the interactions between tumor cells and immune cells are complex and thus enhanced HMGB1 expression may cause resistance to radiotherapy in certain tumor entities as recently shown for bladder carcinoma.[32,33]

3.3. Irreversible electroporation (IRE)

Irreversible electroporation (IRE) involves the application of an electric field across the cell membrane to increase its permeability. Studies on dogs using IRE to target the prostate gland revealed that a reaction was noted in the draining lymph nodes, suggesting a possible immune stimulation.[34] Li et al.[35] provided evidence of change in cellular immunity with an increase in CD4/CD8 ratio in an osteosarcoma rat model. Furthermore, levels of IL-10, an immunosuppressive cytokine, were shown to decrease.

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