Potential therapeutic benefits stemming from the thermal nature of irreversible electroporation of solid cancers

To the Editor:

Irreversible electroporation (IRE) is a CE- and FDA-approved treatment modality for pancreatic and liver tumors that is based on the site-confined destruction of tumor tissue by multiple short, high-intensity electrical pulses.[1] Currently there is a heated debate about whether the therapy is thermal or non-thermal. The 'non-thermal proponents' advocate that thermal evolution does occur to a limited extent but plays no important role[1] or is absent altogether, as advertised by some distributors of IRE instruments (Fig. 1). The 'thermal proponents' claim that the therapeutic effect of IRE stems in part from the consequences of heating.[2, 3] In our opinion, IRE has an important thermal component[3, 4] that contributes to treatment outcome. In addition to direct tumor destruction by heat, we believe that Joule heating during IRE is indirectly beneficial to treatment outcome due to the anti-tumor immune response induced by heating, as is elaborated in this letter.

Recently we published a study in which the thermal dynamics of IRE in non-vascularized and vascularized tissue was explained through several mathematical approximations.[2] The main conclusion was that, at the clinically employed settings, IRE-induced Joule heating mainly affects perivascular tissue, whereby the temperatures that can be generated range between 67-92 ℃. Moreover, the larger blood vessels that are located in the electrical field are expected to remain patent due to heat convection, as has also been shown experimentally.[5] The residual patency of larger vascular structures is particularly important for the pancreas, which is more susceptible to the consequences of vascular occlusion than for example, the liver.

As IRE is overtly promoted as a non-thermal cancer therapy, our report[2] triggered some dismay among the 'non-thermal proponents'. However, in our opinion, Joule heating during IRE may be a potentially beneficial side-effect of IRE that promotes the immunological removal of residual viable tumor cells after treatment. Thermally-induced cell death may lead to sterile inflammation[6] and an anti-tumor immune response, as has also been described for modalities such as photodynamic therapy[7] and radiotherapy.[8] As evidenced from the histological image taken of a porcine liver following IRE (Fig. 2), IRE-afflicted tissue is characterized by coagulative necrosis, underscoring the manifestation of extensive cell death as a result of IRE, although it is not clear whether the histological damage in Fig. 2 was caused by an electrical field or heat. In case of heat evolution during IRE,[3] heat-induced cell death is expected to encompass thermal denaturation of proteins and subsequent necrosis (severe heating), apoptosis/necroptosis, and autophagy (milder heating) (Fig. 2). All modes of cell death, whether thermally or electrically induced, are accompanied by the release of damage-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs), both of which have important functions in triggering an innate and adaptive immune response. The DAMPs and denatured proteins chemotactically recruit cells of the innate immune system to remove the dead and dying tumor cells, facilitate tissue remodeling, and amplify

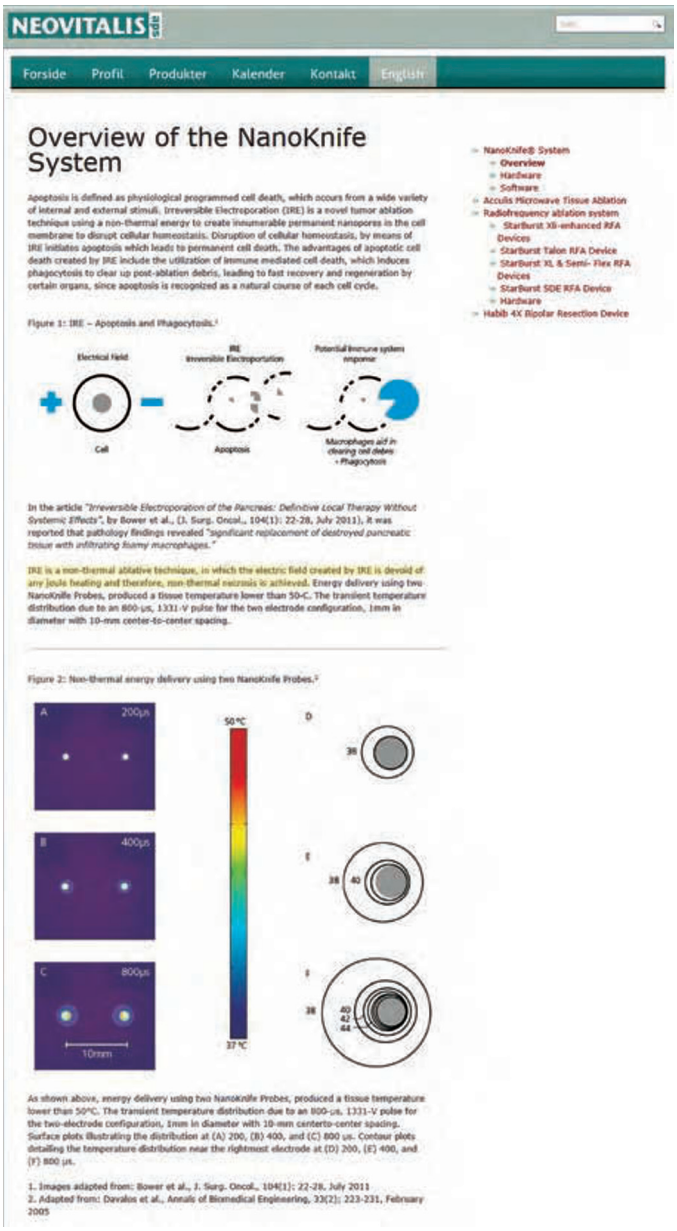

Fig. 1. Screenshot of the NEOVITALIS website on which the NanoKnife system is advertised as being non-thermal (highlighted text). The company is a reseller of the NanoKnife system, which is used for IRE. Source: http://www.neovitalis.dk/benefits.htm, accessed on 22 Nov 2014, 1:50 pm.

the overall immune response (Fig. 2).[6] With respect to the innate immune response, the TAAs are picked up by dendritic cells (antigen-presenting cells) that process the antigens and relay respective immune signals to $CD8^+$ T-cells, which subsequently host an anti-tumor immune response to eliminate the tumor cells that fit the antigen signature profile (Fig. 2). The adaptive immune response may also trigger so-called abscopal effects,[9] whereby distal, non-treated tumor cells are eliminated on the basis of IRE-mediated immunorecognition. Abscopal effects are beneficial for therapeutic outcome.[9]

Vascular patency is not only critical for the sustenance of peri- and post-operative organ function and, in case of hepatic and pancreatic tumors, patient survival, but also for effectively orchestrating the immune response. Retention of blood flow after IRE provides a conduit for the DAMPs and TAAs to rapidly reach their target cells and orchestrate an anti-tumor immune response before afflicted-but-still-viable tumor cells can recover from the treatment. Cancer cells can execute several survival pathways in response to treatment-induced stress that account for a tumor's recalcitrance to therapy and tumor recurrence.[10] Accordingly, the non-thermal as well as the thermal effects of IRE trigger the release of pro-inflammatory, anti-cancer mediators while the vasculature-saving nature of the treatment ensures organ viability and optimal immune signaling. Evidently, these combined effects distinguish IRE from other thermal therapies such as radiofrequency ablation and hyperthermia, which work solely on the basis of considerable Joule heating.

On a final note, pre-surgical planning that involves IRE should always focus on proper perioperative thermal management, whereby controlled thermal evolution should be embraced for its potentially therapy-enhancing effects rather than shunned to distinguish IRE from alternative thermal therapies. In that respect, our previous message regarding the thermal nature of IRE[2] should not be taken lightly in juxtaposition to what has been published[1] and advertised (Fig. 1), as thermal effects may have undesired clinical consequences. Furthermore, the postulations in this letter regarding the IRE-induced immune response are yet to be demonstrated clinically, in anticipation of which we have started a clinical trial (NTR4230) in which DAMPs and TAAs will be quantified before and after IRE. Finally, the thermal nature of IRE opens up novel treatment avenues. A possible combinatorial modality may entail for example IRE with the concomitant use of doxorubicin-containing thermosensitive liposomes or hydrogels, whereby the doxorubicin is released upon elevation of the temperature to a few degrees Celsius above body temperature in the target tissue. More recently, our department (Department of Pharmaceutics in Utrecht) has developed hydrogel-based embolization material that contains doxorubicin-encapsulating thermosensitive liposomes. This material can be used to embolize tumors which are subsequently subjected to IRE, thus inducing the release of liposome-laden chemotherapeutics as an adjuvant form of therapy. Taken altogether,

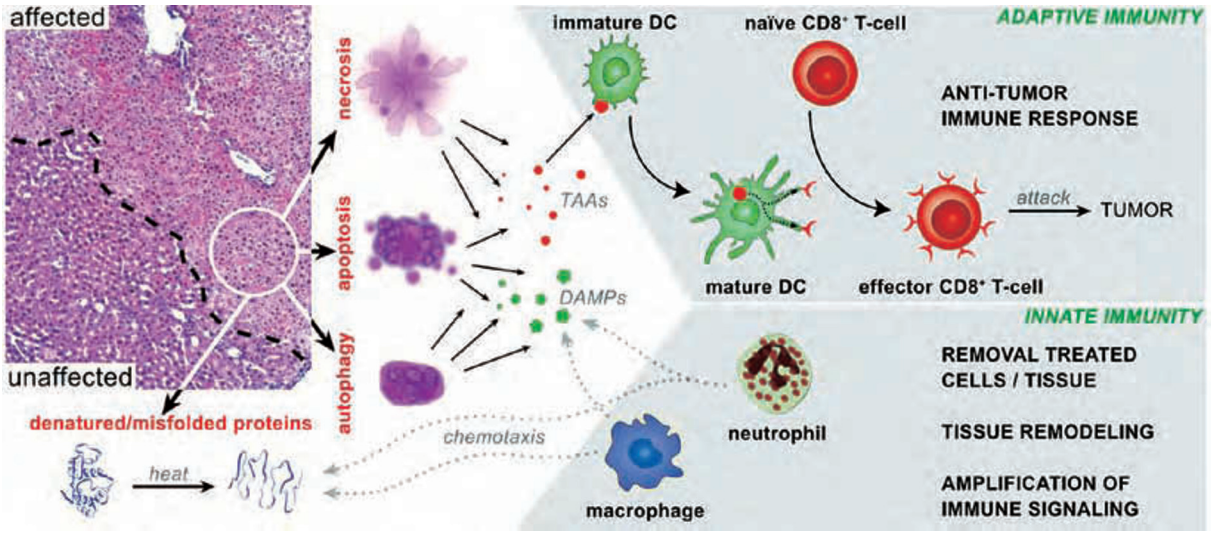

Fig. 2. Mechanistic explanation of the proposed IRE-mediated immune response. The histological section displays liver tissue in native state ("unaffected") and a tissue segment affected by IRE ("affected") (adapted from IEEE Trans Biomed Eng 2006;53(7):1409-1415), separated by the dashed line. IRE-mediated Joule heating as well as electrical effects cause protein denaturation and the induction of various forms of cell death (necrotic, apoptotic/necroptotic, autophagic), which leads to the release of damage-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs). The DAMPs facilitate chemotaxis of neutrophils and macrophages to the treated region, which leads to the effects specified under "INNATE IMMUNITY". The TAAs are processed by cells of the adaptive immune system that subsequently mount an anti-tumor immune response to eliminate the tumor cells, which may include abscopal effects.

the fact that IRE is a heat-producing modality comes with potential clinical drawbacks but also clinical benefits and paves the way for novel therapeutic approaches.

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