COST BM 1309 "EMF-MED"

Proposal for a Working Module (WM) on "*Microwave thermal ablation for cancer therapy*"

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WM topic and description

Microwave thermal ablation (MTA) is an EMF-based therapeutic technique offering the possibility of destroying relative large tissue areas with minimally invasive applicators and thus showing many promising advantages for local treatment of soft-tissue pathologies, as tumours. MTA exploits the irreversible cellular damage due to high temperature heating (exceeding 55-50 °C) induced by the absorption of electromagnetic energy at microwave (MW) frequencies.
The implementation of treatment planning procedures for the clinical practice requires the development of patient-specific simulation models, exploiting the availability of high-resolution digital models (e.g. from magnetic resonance or computerised tomography scanners) and automated tools for the generation of the electromagnetic (EM) model. However, before accomplishing this goal, there are still several open issues to be investigated, with particular reference to the changes in the dielectric, thermal and morphologic properties of tissues due to the very high temperatures reached during a MTA treatment. Deep understanding of these phenomena could allow the development of optimised ablation antennas and of predictive tools for personalised treatment planning in clinical practice.
The proposed WM "*Microwave thermal ablation for cancer therapy*", within the WG1 (Cancer EMF interactions and applications), aims at building up a multidisciplinary network of experts including researchers, clinicians and technical specialists, in order to promote synergistic research on specific topics concerning MTA for cancer therapy, and to propose novel methodologies and solutions for improving clinical applications and quality assurance. The WM activity could be developed ideally over the Action lifetime.

Comprehensive review of the research (state-of-the-art)

MTA is a minimally invasive therapeutic technique used to destroy un-healthy tissue by way of a very high and localized temperature increase, induced by the absorption of EM energy at microwave (MW) frequencies [Goldberg *et al*, 2000, Ahmed *et al*, 2011; Ryan *et al*, 2010; Chiang *et al*, 2013]. MTA has remarkably developed in the last years. Nowadays it is largely employed as a minimally-invasive therapy for potential eradication of hepatocellular carcinoma (HCC) and other secondary liver tumours (with particular reference to colorectal cancer metastasis) in non-surgical patients [Hamazoe *et al*, 1995; Livraghi *et al*, 2001; Feliberti and Wagman, 2006; Schwartz *et al*, 2007; Callstrom and Charboneau, 2008;]. About fifteen thousand clinical procedures (RF/MW) are performed every year in Western Europe, and over a hundred thousand per year world-wide, with a rapidly increasing trend for MW ablation procedures.

In tumour ablation procedures, MTA treatment planning is based on the definition of the MW power to be radiated by the antenna, and on the time of irradiation needed to achieve an ablated zone, also named thermal lesion, sufficiently wide to cover all the cancerous tissue plus a safety margin. MTA is able to achieve thermal lesions with radial extension up to 5 - 6 cm from the MW antenna [Cavagnaro *et al*, 2011]. This extension allows to treat soft-tissue pathologies, such as tumours, having dimensions up to 3 - 5 cm with a 0.5- to 1-cm margin of apparently healthy tissue, to eliminate microscopic foci of disease and to compensate for the uncertainty that often exists regarding the precise location of actual tumour margins [Ahmed *et al*, 2011].

The MW applicator consists in an interstitial antenna, inserted into the body to the target area following natural paths (veins, orifices) or percutaneously. Several factors influence the outcomes of MTA procedures, as the correct position of the antenna within the tissue to be treated, the tissue composition, the presence of blood vessels, and the reactivity of treated tissue or organ. Moreover, the very high temperatures, up to 100 – 120 °C, reached in the target tissue lead to modifications of the tissue's electric, thermal and morphological properties. All these factors may influence the optimal power or time of irradiation to be used in the procedure. Accordingly, in the clinical practice the implementation of MTA treatment planning as well as of the real time check of the outcome of the treatment still presents challenging issues, calling for the development of minimally invasive methods for real time monitoring of the tissue's temperature.

The placement of the antenna in the centre of the pathologic volume to be treated can be performed under computerised tomography (CT), sonography, or magnetic resonance imaging (MRI). The same techniques could be used for real time monitoring of the temperature increase. However, MRI requires ablation equipment compatible with the magnetic field associated with the technique, sonography is blinded by the hyper-echogenic focus that follows the formation of gas micro-bubbles close to the MW antenna, and CT sees a region of hypo-attenuation at the margin of the treated zone, which lowers the efficacy of the technique in assessing the achieved thermal lesion [Goldberg *et al*, 2000]. Accordingly, the usual clinical arrangement is based on temperature sensors placed around the area to be treated and close to critical organs, in order to ensure a safe level of temperature increase in such positions [Ren *et al*, 2011].

For the development of reliable clinical protocols, the characterization of the MW antenna [Lopresto et al, 2012a], and the reproduction of the physical processes associated with the heating of the target tissue during the treatment is needed. The latter point is particularly challenging, due to the many phenomena occurring at the temperatures typical of MTA: in a temperature range of 60 - 80 °C protein denaturation occurs [Chin and Sherar, 2001; Bircan and Barringer,2002], whereas as temperature approaches 100 °C tissue's water content drops due to the generation of water vapour and to the diffusion of water from the treated cells [Yang et al, 2007a]. These structural modifications lead to changes in both dielectric and thermal properties of the tissue with increasing temperature, followed by a change of the EM power deposition, of the heat conduction within the tissue, and eventually of the size and shape of the induced thermal lesion [Ji and Brace, 2011; Lopresto et al, 2012b; Ai et al, 2012; Yang et al, 2007b]. In [Ji and Brace, 2011; Lopresto *et al*, 2012b; Lopresto *et al*, 2014] the dielectric properties of *ex vivo* liver tissue undergoing MTA procedures were measured, and numerical models of the changes of relative permittivity and electric conductivity with the temperature were proposed. Other studies were devoted to the characterization of the tissues' specific heat as a function of the temperature [Ramachandran *et al*, 1996; Haemmerich *et al*, 2006; Yang *et al*, 2007a; Yang *et al*, 2007b]. Little information is available on the thermal conductivity changes with the temperature, particularly with reference to

data measured during MTA trials. Numerical studies modelled the thermal conductivity dependence on the temperature with a constant behaviour [Yang *et al*, 2007b], a continuous increase [Keangin *et al*, 2011], a piece-wise increase [Ai *et al*, 2012], and a non-monotonic behaviour [Lu *et al*, 2009]. Moreover, several papers recently pointed out the presence of a contraction phenomenon linked to the very high temperatures reached by the tissue during a MTA procedure [Brace *et al*, 2010; Sommer *et al*, 2013; Rossmann *et al*, 2014]. The contraction leads the ablated tissue to occupy a volume that corresponds to a greater zone of the untreated tissue, yielding to underestimate the extent of the original tissue included in the ablated zone; such a phenomenon can be particularly emphasized for high amount of deployed energy.

Finally, the thermal dose required to achieve tissue coagulation is still a controversial issue. In [Mertyna *et al*, 2008; Mertyna *et al*, 2009] both *ex vivo* and *in vivo* models were considered as well as different energy ablation sources. Results evidenced that the thermal dosimetry of ablation cannot be based on a fixed end temperature at the margin of the coagulation zone, as tissues subject to thermal ablation may exhibit a wide range of thermal sensitivity; potential modifying effects of the rate of heat transfer and of the intensity of electromagnetic energy should therefore be taken into account for ablation dosimetry.

One of the reasons limiting MTA clinical use, especially in large lesions, is the extent of the inflammatory reactions induced by the necrotized tissue. Indeed extended MTA has been recognized as a risk factor for the occurrence of post-treatment complications and the post-ablation syndrome [Mulier *et al*, 2002; Livraghi *et al*, 2003]. On the other hand, MTA has been also shown to induce positive effects on anti-tumour immunity [Shinichi *et al*, 2013] indicating the possibility to develop combined therapies.

Gaps and challenges

As from the review of the state of the art, several gaps remain to be considered for a full development of MTA techniques, as e.g. the changes in the dielectric and thermal properties, tissue shrinkage, temperature monitoring, etc. Most of the studies separately investigated the different physical processes, as well as possible mechanistic effects of the rate of heat transfer on induced coagulation in different tissues. However, being the power density deposition within the tissue strictly linked to the peculiar MW antenna used, it is extremely difficult to draw general rules from these sparse data. As an example, the general consensus on the best frequency to be used is still lacking. Moreover, a thoroughly analysis of the thermal sensitivity from various tissues is needed, as well as further studies to allow greater discrimination between the effects of tissue's electrical and thermal parameters on thermal dosimetry of ablation. Deeper and systematic understanding of all the issues linked to MTA are essential in order to improve the quality of MTA protocols in the research as well as to promote translation of the research results to the clinical practice as well as for establishing robust thermal dosimetry methods acknowledged both by the research and the clinical community.

The possibility of acute systemic inflammatory reactions as well as long-term effects due to prolonged/chronic inflammatory responses can induce relevant side effects. On the other hand positive effects on anti-tumour immune responses have been also described. Understanding the underlying mechanisms responsible for these two sides one coin phenomena is still an unmet issue that should be addressed also in view of the possibility to develop combined therapies for

improving MTA clinical use and effectiveness [Mulier *et al*, 2002, Livraghi *et al*, 2003; Shinichi *et al*, 2013; Rosado *et al*, 2013].

Goals to be achieved

Aim of the proposed WM "*Microwave thermal ablation for cancer therapy*" should be to build up a multidisciplinary network of experts with researchers, clinicians and technical specialists; the WM activity could be developed ideally over the Action lifetime. The goals to be achieved could include:

- extensive review on the state of the art of the research and of the clinical practice;
- promotion and establishment of new links with industrial partners, by converging academic, clinical, and industrial research;
- development of robust real-time thermal dosimetry methods for improving clinical applications;
- analyses and development of methods for the evaluation of local and systemic inflammatory responses and effects on anti-tumour immunity;
- provide inputs and recommendations for quality assurance in the research and clinical practice.
- identification of eventual further specific research needs and "hot topics" to be synergistically investigated.

Proposed research activities

Investigations should be performed starting from *ex vivo* tissue models and then moving to *in vivo,* considering different organ sites, to better address the wide range of clinical applications.
Proposed research and activities would include:

- extensive review on the state of the art of the research and of the clinical practice;
- investigation on differences in the dielectric and thermal properties of healthy and malignant tissues;
- characterisation of changes in the dielectric and thermal properties of tissues with the temperature;
- development of a comparison among the different MTA techniques and frequencies used;
- investigation on thermal sensitivity of tissues and thermal dose for tissue coagulation (both *ex vivo* and *in vivo* models should be considered);
- development of robust real-time thermal dosimetry methods for improving clinical applications;
- development of methods for the evaluation of local and systemic inflammatory responses and effects on anti-tumour immunity;
- establishing minimal recommendations for quality assurance in the research and clinical practice.

From the synergistic discussion among the involved experts, further research needs should be identified and proposed for investigation.

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