Cost EMF-MED (Split meeting 2-3 October 2014)

Workgroup 1: Cancer EMF interactions and applications
WM topic: High Level EMF in Cancer Treatment
WM title: Focused EMF hyperthermia with online guidance and improved dose models
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WM description
The development of low toxicity treatments is of major relevance as in the coming decade the incidence of cancer in elderly patients in Europe will dramatically increase. Many of these patients cannot tolerate the highly aggressive radio- or chemotherapy schedules required to control locally advanced tumors due to unacceptable levels of toxicity. As the continuously improving effectiveness of cancer treatments, may turn cancer into a chronic disease many patients will require repeated treatment.

Adjuvant thermal therapy is a promising approach to increase the efficacy of existing radio- and chemotherapy protocols, as extensive biologic research has shown that hyperthermia is the most potent sensitizer of radio- and chemotherapy known today [1,2,3]. The fact that in clinical trials, hyperthermia has shown not to increase toxicity is a major drive to invest in developing innovative devices and applicators to deliver thermal therapies [4,5]. In addition, the recent demonstrated ability of hyperthermia to decrease the repair of DNA double strand breaks provides a gateway to new treatments strategies involving hyperthermia [6]. In combination with temperature sensitive drug carriers hyperthermia can be used for triggered local drug delivery [7].

A major bottleneck hampering clinical use of HT is the perceived difficulty in the application of high quality heating. As a consequence wide clinical implementation of hyperthermia is hampered by the fact that many oncologists consider hyperthermia a complicated and difficult to apply treatment. Most importantly during the last two decades many studies reported statistical significant relationships between applied thermal dose and treatment effectiveness, i.e. tumor control and even survival. Especially convincing are the prospective study of Jones et al. [8] and the large, retrospective study of Franckena et al. [9]. Together, these studies demonstrate a clear rationale to develop methods for escalation of the applied thermal dose
and thus the need for technological innovative systems able to deliver personalized adaptive hyperthermia treatments.

This module will seek solutions for the application of focused adaptive EMF hyperthermia as a reliable, reproducible and straightforward clinical procedure with integrated online guidance of the thermal dose delivery.

State of art
The ideal hyperthermia system provides homogenous tumor heating at 43°C and 60 minutes, for which it adaptively deposits electromagnetic energy in tissue under real-time 3D temperature feedback control. In reality current hyperthermia systems are still far away from this ideal situation [10,11]. Over the years devices for hyperthermia have been innovated aiming at reduced size, flexibility and output control. For deep hyperthermia the applicators are mostly rigidly constructed, whereas for superficial hyperthermia, the applicator has evolved from a rigid “one size (design, device) fits all” antenna to multi-element arrays offering flexibility to follow the contour of the treatment area.

In general two frequency ranges of the EMF can be discerned according to the depth extension of the tumor. For superficial hyperthermia (tumor depth less than 4 cm from the tissue surface) the frequency of choice is 434 MHz in Europe and 915 MHz in the USA (I.S.M. frequency bands). For deep hyperthermia (tumor depth >4 cm) the applied frequency is between 70-120 MHz. Distinct differences between hyperthermia systems are incoherent or coherent operation of the EMF for superficial or deep hyperthermia, respectively. In superficial hyperthermia coherent use is considered not necessary as coherency will only marginally improve penetration depth, while spatial control is more dictated by the antenna size and their number. Contrary for deep hyperthermia creating a circumferential E-field distribution with constructive interference configured in an annular array type applicator strongly contributes to improved energy deposition at depth. Frequency and applicator size are also determinative for the focus size, thus spatial resolution. With the available deep hyperthermia systems operating at 70 to 120 MHz, the heating focus has a diameter ranging from 15 to 11 cm and an axial length of 15 to 22 cm [12,13].

Clinical experience in hundreds of patients treated with these first design systems show that deep hyperthermia at 42 °C is feasible, however, two major limitations exist [14,15]:
1. The height of - and duration at - the target temperature is often restricted by pain complaints of the patients caused by too high temperatures in normal tissue. Unfortunately, the occurrences of these hot spots are closely related to the anatomy of the patient and the consequence of using a low frequency. Moreover, the rather large focus of the low frequency also prohibits small scale adjustment of the RF energy. Hence, current deep
hyperthermia systems provide only a very limited ability to adequately counteract hot-spot complaints or optimize temperature uniformity in the tumor volume.

2. Current application of deep EMF hyperthermia lacks a true feedback on the amount of delivered energy, i.e. the practitioner needs to rely on experience and limited metrology to observe achievement of the treatment targets. To solve this problem a hybrid deep hyperthermia system has been developed in which a BSD2000 Sigma Eye applicator is integrated within an MRI, enabling seamlessly 3D-temperature imaging during heating of the tumor. Combining 3D temperature monitoring with advanced hyperthermia treatment planning (temperature and energy distributions) paves the way towards the application of on-line controlled adaptive hyperthermia if the spatial resolution of the energy deposition can be improved [16,17,18,19,20].

Gaps and challenges
The two limitations on current deep hyperthermia systems as defined above are in sharp contrast to the clinical needs. From a medical and patients point view several strong arguments exist to invest in designing innovative hyperthermia systems, i.e. systems with a sharper heating focus and a better spatial and temporal control:

1. Existing thermal dose effect relationships clearly demonstrate a higher probability of tumor control (cure) with higher thermal dose.

2. Lower probability of toxicity due to better control of hot-spots, which is accompanied by improved patient comfort and tolerance for the treatment.

3. Introduce the possibility of treating two tumors different locations (primary tumor locations and involved lymph nodes).

4. Improved specificity of tumor heating will allow to reduce the time interval between radiotherapy and hyperthermia. A shorter time interval is expected to result in a higher radio-sensitization of the tumor by hyperthermia and thus resulting in more cell kill.

5. Enables more precise temperature triggered drug delivery.

Objectives to be achieved
The only way to improve the quality of the hyperthermia treatment by enhanced small scale EMF energy deposition in the human body is to design hyperthermia systems operating at higher frequencies (200-500 MHz), while counteracting the reduced penetration depth by substantially increasing the number of sources.

A distinct disadvantage of a high number of antennas is the increased complexity to control the delivered RF-energy absorption pattern. The control is of the RF-energy absorption pattern is affected by the anatomical variation (amount of skin, fat, muscle, tumor, etc), with each tissue having its own permittivity and perfusion values that affect the obtained temperature increase. For a good spatial control of the resulting temperature distribution the RF-energy absorption
pattern needs to be controlled with a resolution of a few (2-3) cm. At the same time target area or target volume can be very large. This translates in applicator with 50-100 (up to 200) antenna elements. Each element needs its own amplitude and phase controlled RF-signal. Using many small elements will reduce the requirement of RF-power output per element but due to power losses in cables, antennas; reflection at the tissue surface; compensation for heat loss by blood perfusion; and heat loss by heat conduction still a substantial power output (20-50 W, cw) per RF-signal will be required.
A major disadvantage of a high number of elements is the cross-talk that will exists within a multi-element array. Solutions need to be implemented to neutralize the impact of the cross talk. At the same time the control of the heating pattern, stationary or dynamically scanned through the target volume, will require excellent guidance in the correct settings of amplitude and phase of the RF-signal submitted to each antenna element.
As indicated, clinical exploitation of these features requires the integrated use of 3-D, non-invasive temperature monitoring by MRI parallel with accurate patient specific, on-line hyperthermia treatment planning for both energy and temperature distributions.

Proposed research activities
Widespread application of RF-driven hyperthermia treatment requires innovative approaches enabling controlled and easy to apply delivery of a controlled high quality heat treatment with minimal human interfacing.
This requires technological development of:
- Coherent arrays of thin, high density RF-applicators integrated in easy to apply, flexible technology.
- Automatic, fast, and patient-specific hyperthermia treatment-planning platform.
- Robust volumetric MR temperature measurement techniques
- Time-modulated steering for achieving target-conformal and homogeneous heating.
- Electric field sensors to measure the magnitude and phase of the E-field in the water bolus.
- Development of advanced temperature and E-field sensing systems for building an intelligent feedback system to automatically control localized heating of the target.
- Feedback loop to correct for deviations between the measured and predicted field per antenna.

The combination of these features will enable a breakthrough in the application of hyperthermia in cancer treatment. Realization of this breakthrough provides the clinician with the important tool to translate from the current ‘dump and pray’ hyperthermia to a standard of care comparable with that in radiation oncology. By this, the clinician is given tools for pre-treatment decision making based on hyperthermia treatment planning, on-line viewing and registration of the delivered quality of the treatment.
References


