Towards target conformal RF-hyperthermia: a clinical perspective

Margarethus M. Paulides
[1]Erasmus MC Cancer Institute, Department of Radiation Oncology, Hyperthermia Unit,
P.O. Box 5201, 3008 AE Rotterdam, the Netherlands, m.paulides@erasmusmc.nl

INTRODUCTION

The number of patients that die of cancer increases each year and surviving patients suffer from the tremendous side-effects of standard treatments, like radiotherapy and chemotherapy. Phase III clinical studies showed that hyperthermia (heating to 40-44°C for one hour) selectively sensitizes tumor cells to radio- and chemotherapy. Despite these encouraging results, temperatures achieved in the target region are restricted by stray radiation in normal tissues. In addition, analysis of clinical data has shown that outcome can be improved when higher temperatures are obtained. Hence, more focused heating would allow to increase target temperature while keeping the temperature in normal tissues at an acceptable level. Even more focused heating, i.e. target conformal hyperthermia, would provide an additional option. Such spatially selective heating, i.e. restricting normal tissue temperature increases, provides a window of opportunities for optimizing the time delay applied between DNA damaging agents, like ionizing radiation and drugs, and the adjuvant hyperthermia treatment. Pre-clinical studies indicate that a tremendously increased sensitization of the ionizing radiation can be obtained, i.e. from 1.3 to 5-fold times the applied ionizing radiation dose. In view of the clinical demand, such technology that allows to tailor the heat focus to the target region is highly desired.

STATE OF THE ART

Current state-of-the-art hyperthermia devices are based on radiofrequency “radiative” techniques. These systems operate at 70-130MHz and provide large heating zones. In addition, this technology does not allow counteracting the strong thermal gradients in inhomogeneous tissue. On the other hand, the small focus allowed by high intensity focused ultrasound (HIFU) provides only a solution for a small subgroup of patients with small tumors. Hence, devises with improved focusing capabilities are warranted.

Even if precise heating is feasible, such technology should also be guided using accurate treatment quality control. The tremendous and inhomogeneous cooling strongly modulates the heating pattern that require correction. In most clinical applications, temperature probes inserted into closed-tip catheters, placed in body cavities (“intraluminal”) or pierced into tissue (“interstitial”), are used for assessment of the thermal dose. Although accurate, such thermometry provides limited spatial information and these measurements are influenced by tissue contact (intraluminal) or the risks associated to their placement (interstitial). Current state-of-the-art in control is by using non-invasive magnetic resonance (MR) thermometry (MRT) measurements. This step requires integration of hyperthermia applicators into an MR scanner, which is far from trivial but has been shown feasible by several groups. Still, MRT is distorted by patient- and scanner-induced errors, i.e. motion (cardiac, respiratory) and magnetic field drift. In case of high-temperature small-focus ablation, techniques have been developed to overcome these issues but for hyperthermia these items remain unresolved. Hence, control beyond the state-of-the-art level is required for target conformal hyperthermia.

OPPORTUNITIES

Physics dictates that more focused heating is achievable by increasing the operating frequency of the applied electromagnetic waves and hence reducing the wavelength. This improvement is however at the cost of reduced penetration of the waves into the tissues. This can be counteracted by exploiting the quadratic increase in interference by the waves of additional electromagnetic sources. Therefore, we started exploring the use of "focused microwaves" (FoM) for generating smaller heat focus sizes in a semi-deep setting, i.e. the head and neck region. Based on extensive modelling studies, we could show that 434MHz FoM using sufficient channels (>10) allows target conformal heating in the challenging head and neck region. In follow-up studies we investigated the use of higher frequencies also for hyperthermia in the pelvic region. Simulation studies did show the feasibility of this step but also clearly demonstrated that even more sources are required.

Control beyond the state-of-the-art level can be achieved by supplementing the MR measurements by accurate electromagnetic and thermal simulations. Clinically, we already demonstrated the strong potential of those simulations in an adaptive approach. In this approach, hotspots (high measured temperatures or complaints by the patient) are converted into locations where power absorption should be reduced. Supplementing the 3D temperature maps of MR with this information potentially could replace the role of the patient. In addition, the addition of simulations would make it possible to achieve highly reliable temperature maps also in regions where confounders decrease MR measurement accuracy. Hereto, advanced model based feedback and control must be implemented. Recently, we showed the feasibility of this approach in a study, in which we combined simulations with invasively measured temperatures. Already based on the sparse data provided by the probes, we could demonstrate thermal dose monitoring accuracy of within 0.4°C.

CONCLUSION

The foundations for target conformal RF hyperthermia are in place. Now is the time for a multi-modality multi-center approach for developing the technology that pushes the boundaries and provides the desperately needed solution for the clinic.