

LETTER TO THE EDITOR

Towards developing effective hyperthermia treatment for tumours in the nasopharyngeal region

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We would like to start by congratulating Hue et al. [1] with the positive results in their phase III trial, which illustrates once more the potential of hyperthermia (HT) for treatment of cancer in the head and neck (H&N) region. Treatment of cancer in the H&N region with the current standard treatment of standard radio-chemotherapy (RCT) is complex [2], and loco-regional control poses a major therapeutic challenge [3, 4]. RCT generally results in a 5-year survival rate of 20–65% [2]. Optimised radiotherapy and patient selection may provide opportunities for optimising the therapeutic ratio, as indicated by the review of Corry et al. [5]. However, we feel that the potential role of biological radiation modifiers is missing in this review. Modifiers such as HT have a high potential to provide a faster pathway towards a more selective and cost-effective treatment. Specifically for nasopharyngeal tumours, acceleration of treatment is still desired, with a focus at the gross tumour volume (GTV) [6]. Given the demonstrated ability of HT to enhance treatment outcome when added to RT, without increasing toxicity [7–11], it seems logical to combine RT with HT to improve the therapeutic ratio in the treatment of nasopharyngeal cancer. The phase III study by Hua et al. [1], which studied the influence of intracavitary HT, provides highly important clinical data supporting this rationale to continue research into the benefit of HT in the treatment of tumours in the nasopharynx.

The nasopharynx is characterised by many tissue transitions, cavities of air in the vicinity and highly thermo-sensitive tissues nearby [5]. Applying adequate heating to target areas in the deeply located nasopharyngeal region, therefore, is a challenging task. Hence, we were delighted to see the encouraging results of the study by Hua et al. [1]. In this study, 180 patients with nasopharyngeal cancer were randomised to receive (chemo) radiation either with or without intracavity hyperthermia. This study showed an increase in 5-year survival rate from 81.1% to 95.6% when adding hyperthermia, and an

improvement in local control from 78.9% to 91.1%. Although less spectacular than the improvements reported by Valdagni et al. [12, 13] and Amichetti et al. [8], the results from Hua et al. do confirm the benefit from hyperthermia when added to radiation for this deeply located site in the head and neck region. Equally important was the observation that no increase in early or late toxicity was induced.

Despite the encouraging results, we find it difficult to translate the results of the study [1] for the benefit of further progress. We regret that only limited details are presented from a physics point of view, i.e. limited data on applicator, patient set-up and thermometry are given. More specifically, we have four items that we would appreciate clarification on. Firstly, the authors refer to a commercial applicator, but no link for further information is given. Such data are very important for developing next generation, more selective applicators and hyperthermia techniques. Secondly, the experimental data from measurements with dogs are not available and it is unclear whether the data are used to justify the predictive value of superficial temperature measurements or to support the heating technology. Thirdly, only T90 thermometry data are given and the variation between patients is unclear. Lastly, it is confusing whether the temperatures are measured at the nasopharynx surface or, as suggested later, represent the T90 in the tumour.

In Rotterdam in 2003 we started developing techniques for external heating in the H&N region, including the nasopharynx [14, 15]. Treatments performed thus far have shown the feasibility of deep heating by a non-invasive technique using microwaves [16]. Furthermore, we showed that intratumoural temperature measurements in the nasopharynx are challenging but feasible. Recently, other groups also presented initial work on technology developments for H&N HT [17].

In hyperthermia applicator technology design in general, a 5–10-year cycle can be observed. Firstly, the most advanced hyperthermia system is created

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that in step two is used to perform clinical studies. Step three implies evaluation of the study results that fourthly are converted into the requirements for new hyperthermia technology. For fast progress in hyperthermia application it is essential that these steps are taken rigorously. This implies that clinical data is accompanied by sound thermometry data. The need for sound thermometry measurements is reflected in the various quality assurance guidelines, i.e. Radiation Therapy Oncology Group (RTOG) and European Society for Hyperthermic Oncology (ESHO) guidelines advise invasive thermometry and provide specific guidelines for temperature registration [18–20]. Furthermore, the quality of a hyperthermia treatment has shown important, which is illustrated for the nasopharynx region by the need for coverage for the large (T4) tumours reported by Hua et al. [1]. Quality indicators such as the CEM43°CT90 concept by Thrall et al. [21] and the TRISE concept by Franckena et al. [22] have shown predictive in the treatment of dogs or humans, respectively. However, data from clinical studies in the nasopharyngeal region are required to establish the constraints on heating quality specifically for this site.

The best approach for HT treatment of nasopharyngeal tumours is yet to be determined. This might involve a combination of intracavitary and external heating. Therefore, comparative theoretical or experimental studies are pivotal for developing the optimum treatment equipment and strategy. This process is strongly accelerated when clinical studies are accompanied by detailed information, either simultaneously published or separately, on the used set-up, dosimetry and technology and sufficient thermal data. Hereby, I kindly ask you to provide or publish such data for creating an open dialogue between medical and physics experts that will surely provide an important stimulus to improve the treatment for this poor subset of patients.

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