A Clinically Proven, Prospective, Thermal Dose Descriptor Exists

In Response: We appreciate the consideration that Dr. van der Zee and her group have given to our recent hyperthermia trial in canine sarcomas published in Clinical Cancer Research (1). It is apparent that they have scrutinized our trial very carefully and we welcome this examination. However, we are dismayed by their diminution of the significance of many of the critical points identified in this trial and we are glad to have the opportunity for a reply.

First, a point of clarification. They interpreted the results of our canine trial as, “...a high hyperthermia dose results in more tumor cell death than in a low hyperthermia dose...” We did not make the interpretation that higher thermal doses resulted in more cytotoxicity. Such a mechanistic determination, although very important, was not possible in the trial, which focused on clinical response to treatment. Indeed, cytotoxicity may have been influential, but physiologic changes in the tumor microenvironment are also likely to be a function of thermal dose as well.

We were criticized for not treating tumors deemed to be unheatable. The inability to heat a tumor could have been a result of two problems: (a) there may be technical issues resulting in inadequate energy deposition, or (b) there may be physiologic characteristics of the tumor that prevent deposited energy from being absorbed locally, i.e., high perfusion. In our trial of canine sarcomas, which were relatively superficial, energy deposition was not problematic and the failure to reach our target temperature was thought to be due to high perfusion, although admittedly perfusion was not measured. van der Zee et al. go on to suggest that testing for heatability a priori is unrealistic as it will result in the exclusion of patients who may actually benefit from the procedure. This, again, fails to discriminate between tumors that cannot be heated for technical versus physiologic reasons. Indeed, if one could overcome power deposition problems in deeply seated tumors, more specimens would fall into the heatable category. In a tumor in which maximal power deposition does not result in a suitable temperature increase, the tumor really is physiologically unheatable, and there is no justification for including these patients in a hyperthermia trial; it is a waste of critical resources and is an unnecessary procedure for the patient. Whether to include tumors in hyperthermia trials in which hyperthermia cannot be delivered because of technical reasons is another question.

There was a question regarding the relationship of T10 to other variables. We stated that there was no significant relationship between T10 and any of the outcome variables in our trial. Additionally, data from the trial indicated that there was no significant association between T30 and T10. As treatment duration was based on T30, there would not be an association between treatment duration and T10. To explain the observation of the heating duration effect being negatively associated with local control duration, we hypothesized that tumors with a low T30 could have a high T10 leading to prolonged exposure of a part of the tumor to high temperatures. This is a hypothesis, one not designed to be tested in our prior trial. To test this hypothesis, and others, we have initiated an in-depth study of the physiologic and biological effects of two vastly different fractionation schemes to investigate the consequences of hyperthermia fractionation on tumor response to a defined thermal dose.

It was stated that applying a prospectively prescribed thermal dose in the clinic will be “difficult to realize.” Marcus Aurelius said, “Because a thing seems difficult for you, do not think it impossible for anyone to accomplish.” We believe the technical and logistic issues in adhering to a method that significantly improves outcome must not be the driving force in the clinical administration of hyperthermia. It is our position that patients will be willing to undergo treatments delivering a prescribed thermal dose knowing that the treatment is more likely to be beneficial, rather than accepting a more comfortable treatment that will not be as effective. In our trial of human superficial tumors, it was possible to administer the prescribed thermal dose in the majority of patients (2).

van der Zee comments on the complications associated with the use of invasive thermometry in deeply seated tumors. We acknowledge that indwelling thermometry catheters may lead to complications, but we have shown that complications associated with invasive thermometry using non-indwelling catheters are not as great (3). Given the complex temporal and spatial heterogeneity of intratumoral temperatures, and the proven relationship between temperature and outcome, we do not believe that conduction of hyperthermia in the clinic should be undertaken without measurement of intratumoral temperatures. Surrogate temperatures may be very inaccurate in describing the bioeffect of a hyperthermia treatment. The issues associated with invasive thermometry are the rationale behind our efforts to develop and perfect noninvasive magnetic resonance thermometry methods. Having accurate noninvasive thermometry as a standard part of clinical hyperthermia must be the goal.

Finally, there is the inference that because three to five hyperthermia treatments of fixed duration with maximally achievable temperatures have been shown to be effective in randomized trials, there is no need to go further in refining hyperthermia fractionation. We are always gratified when clinical trials of hyperthermia are positive, but accepting these results as the best that can be done will result in stagnation of the field. For example, if radiation oncologists, and patients, had not gone to the effort of critically assessing the merits of hyperfractionated irradiation, there would be significantly more treatment failures in sites where that approach has been shown to be beneficial.

The group from Daniel den Hoed has made many important contributions to the field of hyperthermia. However, we cannot accept their implication that tumor temperatures should not be measured, that hyperthermia should be delivered to unheatable tumors, and that thermal dose cannot be applied prospectively. We live in a world of evidence-based medicine and we simply cannot ignore the evidence that prospectively defined and
delivered thermal dose, quantified as CEM43°C\textsubscript{T\textsubscript{90}} and based on tumor temperature measurements, is related to outcome; we have shown this in both canine and human tumors. We do not know if a better thermal descriptor exists, or whether there is a universally applicable thermal descriptor. However, we do know that the thermal descriptor CEM43°C\textsubscript{T\textsubscript{90}} is related to outcome. Failure to embrace this concept could derail the impressive progress that has been made with regard to characterizing how hyperthermia can help patients with cancer.

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