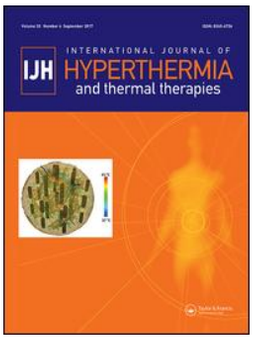

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Letter to the editor

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Letter to the editor

IN REGARD TO THE FOLLOWING PUBLICATIONS

Corry PM, Dewhirst MW. Forward. Thermal medicine, heat shock proteins and cancer. Int J Hyperthermia 2005;21:675–677.
Song CW, Park HJ, Lee CK, Griffin R. Implications of increased tumour blood flow and oxygenation caused by mild temperature hyperthermia in tumour treatment. Int J Hyperthermia 2005;21:761–767.
Corry PM, Armour EP. The heat shock response: Role in radiation biology and cancer therapy. Int J Hyperthermia 2005;21:769–778.
Dewhirst MW, Vujaskovic Z, Jones E, Thrall D. Re-setting the biologic rationale for thermal therapy. Int J Hyperthermia 2005;21:779–790.

Hyperthermia dose and schedule: No evidence yet for changing treatment design

The *Int J Hyperthermia* of December 2005, summarizing the workshop 'Thermal medicine, heat shock proteins and cancer', presents an excellent overview of the state-of-the art of hyperthermia (HT) and ongoing developments. However, the suggestions in four of the contributions of this issue [1–4] on an alteration in HT prescription, although carefully presented, may easily be misunderstood. For example, it may stimulate newcomers in the field to limit the application of HT to too low temperatures. The authors state that future experimentation is required to evaluate the presented hypotheses on more effective treatment strategies, with which we fully agree, but also that the conventional approaches have led to sub-optimal protocol design, for which we find no convincing arguments.

In their argumentation the authors use the observed clinical temperature distribution as support for their advanced understanding on how the improvement in clinical outcome by adding HT to radiotherapy (RT) is achieved. Unfortunately, we miss in their argumentation a discussion on the fraction of high temperatures, T_{max} or T_{10}, within tumour tissue and their potential contribution to the clinical outcome. In this respect we like to stress that the current more positive attitude towards HT is achieved thanks to the positive results of phase III trials comparing RT with RT plus HT. The HT treatment in these trials was applied according to the conventional protocol design and the results provide the most valuable proof we now have on the effectiveness of HT. Only when similar convincing proof exists for the treatment strategies as proposed (mild temperature HT, more frequently than once or twice per week and HT before RT), adaptation to these new strategies is justified. In the following we discuss more specifically the three proposed changes in treatment design with data that support our current, conventional, strategy.

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Why not prescribe mild temperature hyperthermia?

It is true that during externally applied local or locoregional HT the temperature goal of 1 h at 43°C cannot be achieved in the whole volume at risk. The temperature distribution will always be inhomogeneous. In clinical studies, the measured coldest spot in the tumour usually is ~39–40°C.

At the same time, a large fraction of the tumour is at higher temperatures, e.g. in a group of 87 patients with recurrent breast cancer, we found a median tumour T_{90} of 39.0°C (median six intra-tumour measurements; unpublished data). These very low values were achieved by aiming to get the tumour temperatures as high as possible, while keeping normal tissue temperatures within tolerance limits. The median tumour T_{max} in this patient group was 43.2°C, which is a temperature of which a cytotoxic effect can be expected. This HT, in addition to reirradiation with eight fractions of 4 Gy, resulted in 83% local tumour control, where this was ~40% in a comparable patient group treated with the same RT alone [5].

At present we are not sure how the clinically observed effect of HT can be explained. Several effects have been described: direct cell kill at higher temperatures, vascular damage resulting in secondary cell death, enhancement of RT effects by influencing repair mechanisms, improvement of perfusion and oxygenation which results in a better effect of radiation and stimulation of the immune system [4]. These effects become apparent at different temperatures and all these effects may contribute to the desired eventual effect which is, certainly when combined with RT, the achievement of local control. For several of these effects, a positive thermal dose-effect has been established.

We do believe that an improved oxygenation may play a role in the effect of HT in patients, but we don't believe that that's the only or the most important effect. So far, to our knowledge, an improved oxygenation has only been observed up to 24 h after HT treatment and is almost completely disappeared after 48 h [6]. So, the results of the ESHO study in breast cancer (complete response rate 39% following RT and 79% following combined treatment [5]) in which RT was applied twice weekly and HT after radiation cannot be explained by an improved oxygenation 24–48 h after HT. Besides, the improvement of oxygenation may be the result of two events: an increase in blood flow and a decrease in oxygen consumption, probably by some degree of heat-induced cell death. Improvement of blood flow 24 h after HT in one tumour model was maximum after treatment of 1 h at 42.5°C [2]. So, for both heat-induced cell death and improvement of blood flow temperatures around 42°C are preferable.

Two papers refer to the study by Jones et al. [7] which they report to have shown evidence of the importance of improved oxygenation and also evidence of a better clinical outcome with lower temperatures [2, 4]. We find this study not really convincing, for the following reasons. In the first place, this is one small study while there are many and larger both animal and clinical studies showing better results with higher HT doses [8, 9]. Secondly, we could not find evidence that the results were better than those reported for chemotherapy alone or radiation plus chemotherapy. We don't think that it is justified to ignore the patients with clinically a partial response or stable disease who had no surgery, so pCR was seen in 3/18 patients (17%), while in the discussed studies 13–29% pCR was found after neo-adjuvant chemotherapy with or without hormonal therapy and 17% pCR after RT plus chemotherapy. From the published data, one might conclude as well that the patients with better perfusion and, therefore, lower temperatures responded better to RT, independent from their HT treatment.

Our main objection against the term 'mild temperature hyperthermia' is that it suggest that we should abandon the policy of trying to get temperatures as high as possible, within

the normal tissue tolerance limits. Because only with this attempt, we get the temperatures which somehow results in benefit to the patients. One might call this 'realistic hyperthermia'. And we might replace the demand of '1 h at 43°C' by '1 h at a temperature as high as tolerable'.

In our view, the finding that good clinical results are obtained in spite of relatively low temperatures in parts of the tumour should not lead to the recommendation of setting the target temperature at lower values. Instead it should be used to assure the medical community that HT applied with the presently available equipment can be beneficial to patients, even without satisfying the conventional demand of 43°C in the whole tumour volume.

Why not apply hyperthermia more frequently than once or twice weekly?

We agree with the authors that the optimal scheduling for HT is not known [3, 4]. We also agree that thermotolerance probably is not a problem in the clinical setting [3, 4]. However, the statement that most of the protocols with sparse HT fractions did not demonstrate benefit for the addition of HT [3] is incorrect. In all randomized studies giving evidence of a benefit from HT, HT was applied once or twice weekly, with a total number of two to 12 treatments. Several randomized clinical studies have investigated the number of treatments. Besides the two studies mentioned in Dewhirst et al. [4], there have been at least four more of such studies [10–13]. In all studies, no difference in complete response probability was found between the two study arms. Our own experience confirms these findings. In 1996, we had to face the problem of inadequate capacity to treat all patients referred to us for superficial HT. Based on the published results of 'more' vs 'fewer' treatments, we decided to change the HT schedule in recurrent breast cancer from twice to once weekly. We compared the results of the four HT treatment group (40 patients) with the historical eight HT treatment group (122 patients) and found no differences: a complete response rate of 69% after eight treatments and 73% after four treatments [14]. These results do not exclude the possibility that the results would have been better with more than eight HT treatments, but to answer that question would require a large randomized trial. Whether the recommendation to apply HT preferably with each radiotherapy fraction would make this treatment economically and clinically acceptable is a further point of concern.

Why not apply hyperthermia before or during radiotherapy?

Many pre-clinical studies have shown that the thermal enhancement ratio (TER) is maximum when HT is applied simultaneously with RT. However, this does not necessarily result in optimum therapeutic gain. With externally applied local HT, the heated volume will include both normal and tumour tissues. Radiosensitization in normal tissues can be as high in normal tissues as in tumour tissues, which than results in no therapeutic gain. Several pre-clinical studies [15–17] have shown that normal tissue radiosensitization is lower when HT follows RT than in the opposite sequence and that the maximum therapeutic gain is achieved when HT is given after RT. In a clinical study, HT given with a time interval of 1–4 h after RT resulted in therapeutic gain, while HT given immediately after RT gave similar enhancement ratio's for tumour response and skin reaction and, thus, no therapeutic gain [18].

Further studies interesting in this debate are the following. *In vitro* studies have shown that the dependence of the TER for the sequence of RT and HT differs per cell line [19] and that radiosensitisation by heat can also be absent when HT preceeds RT [20]. Further, when higher temperatures are applied, resulting in significant cell death, the TER may be higher when HT is given before RT, while the opposite was found for lower temperatures [21, 22].

Certainly this last finding pleads against giving HT at the clinically achieved levels before RT.

One clinical study compared HT before RT to HT after RT in a group of total 87 patients. No significant difference was found between the two sequences, although the complete response rate tended to be higher in patients who received HT after RT. Toxicity was not reported [23].

A negative effect from HT preceding RT may be that distant metastasis is increased. This has been observed in a pre-clinical study, where a single fraction of RT was combined with HT. De Ru [24] reported an incidence of distant metastasis of 2.6% following RT alone, of 16.7% after radiation preceded by HT and of 0% after radiation followed by HT. In one clinical study, investigating the addition of HT to RT in cervix cancer, the incidence of distant metastasis was reported to be higher in the plus HT group (17%) compared to the radiation alone group (4%). In this study, HT preceded RT [25]. On the contrary, the Dutch Deep Hyperthermia Trial, where HT was given after RT, showed a trend of fewer distant metastasis in the plus HT group (19%) compared to the RT alone group (28%) [26, 27].

In conclusion

In the publications [2–4], we have found no arguments to change our local hyperthermia procedure or schedule. For local-regional hyperthermia, we recommend to aim to get the temperatures as high as possible, while keeping the normal tissues within the tolerance levels, and to apply hyperthermia after radiotherapy. Before recommending a larger number of hyperthermia treatments, which would make institutes even more reluctant to invest in hyperthermia equipment and staff than they already are, evidence of a surplus value of a larger number of treatments than one or two per week first has to be demonstrated in clinical trials.

J. van der Zee, M. de Bruijne, & G.C. van Rhoon
Erasmus MC—Daniel den Hoed Cancer Center, PO Box 5201,
3008 AE Rotterdam, The Netherlands
*Tel: *31 10 4391 498. Fax: *31 10 4391 022. Email: j.vanderzee@erasmusmc.nl*

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IN REPLY TO VAN DER ZEE ET AL.

We greatly appreciate the thoughtful comments provided by van der Zee et al. regarding our recent series of papers summarizing a workshop sponsored by the Society of Thermal

Medicine in the Spring of 2005. The papers were written with the goal of stimulating discussion and, to this extent, we achieved the goal that was set.

We need to take a careful look at the field of hyperthermia and not be afraid to challenge existing paradigms, if there is reason to do so. We fully agree that there are numerous positive phase III trials that were conducted based on the biology from the 1970–1980s. Whereas the trials certainly set a bar, they did not result in high probability for cure in any disease—certainly there is room for improvement. There was no intent to criticize any particular group of investigators or any particular approach since we realize that such regimens were based on available information and the practicalities of clinical hyperthermia. In fact, many of us participated in these early trials ourselves. Our main point was that more recent information argues for regimens that are different. However, changing regimens, sequencing etc. in multi-modality cancer therapy is standard practice in the search for improved results. Obviously, changes in the daily practice of hyperthermia should await results of carefully controlled studies, which we hope will emerge as a result of these discussions. We carefully emphasized this point in the papers and do so again here.

Van der Zee et al. assert that previously published phase III trials form the basis of respect for the field. However, it is curious that interest in hyperthermia has not really increased in the last decade as a result of these trials being published. In fact, interest has undergone significant retraction, aside from a few dedicated centres world-wide. One would have a very hard time finding another adjuvant therapy that has shown more promise across the board than hyperthermia has, yet it has not been embraced by the larger oncology community. It was this realization that led, in part, to the publication of our papers that challenged the old paradigms.

We address each of van der Zee et al.'s concerns, using the same subject headings that they used.

Why not prescribe mild temperature hyperthermia?

Here van der Zee et al. take issue with our argument that killing cells with hyperthermia is not a major biological effect of the treatment. They state that cytotoxic temperatures are often achieved during hyperthermia treatment. We agree with this point, but if one takes a careful look at what proportion of cells are killed by heat during a typical hyperthermia treatment session, it is relatively low, even in a case where the median temperature is as high as 43°C (as reported by van der Zee et al.). There are two things to consider here. First, thermal data derived from invasive thermal mapping is linear, whereas the real temperature distribution is three-dimensional. Therefore, a median temperature of 43°C derived from thermal mapping data does not represent 50% of a tumour volume [1]. Using nested isotherms as a simplified approximation, a median temperature of 43°C would represent $(0.5)^3$ or ~12.5% of a tumour volume. More explicitly, Rosner et al. modelled the cytotoxicity of hyperthermia treatments, taking into account the non-uniform temperature distributions that are typically achieved for superficial tumours [2]. This model used modelled SAR data for three different tumour shapes and two different perfusion patterns, integrated into a thermal conduction model to predict realistic isothermal data. The model predicted the degree of cell killing throughout the tumour volume, using *in vitro*-derived hyperthermia cell survival data from CHO cells [3]. The simulations predicted that a 1 h treatment, with a T_{90} of 39°C, would kill no more than 10–20% of cells. It is important to point out that there were temperatures of 43°C within the treatment volume for this fixed T_{90} level. For a fractionated treatment, the highest temperatures would most typically

remain in the same tumour sub-volume, however. Thus, the proportion of tumour cells killed during a fractionated course of 10 hyperthermia fractions would be considerably less than $(0.9)^{10}$ or 35% survival. However, for arguments sake, we could assume that hyperthermia kills 65% of the tumour cells, at best. A typical tumour contains 10^8–10^9 cells, so this amount of cell killing would be insignificant, relative to the total number of cells required to achieve cure. It is important to note that human tumour cells, in general, are more heat resistant than rodent lines, so if anything, the predicted amount of cell kill from a hyperthermia treatment would be even less than what is predicted from the CHO data [4, 5]. It is within this background that we argue that thermal cytotoxicity is not an important effect of hyperthermia treatment.

The important question to ask, then, is what is responsible for the improvement in treatment outcome when hyperthermia is added to radiotherapy? As we outlined in our original review, there are other effects, such as inhibition of DNA damage repair and improvements in oxygenation. Van der Zee et al. takes issue with our hypothesis that changes in oxygenation might be important. They challenge our data in locally advanced breast cancer showing that tumours with improved oxygenation are more likely to achieve a response following thermochemoradiotherapy [6]. Admittedly, these results were based on a small number of patients. If we were relying only on those data, we would have to agree. However, we have two other published reports, in human and canine sarcomas that corroborate the observation in the locally advanced breast cancer series. In 1996 we reported that improvements in pO_2 24 h after heat treatment were associated with increased likelihood for pathologic CR in human patients with soft tissue sarcomas who were treated with thermoradiotherapy [7]. In 2000 we demonstrated in canine tumours that improvements in oxygenation at 24 h post-heating were most often associated with modest temperature elevations (e.g. $T_{50} < 44^\circ$ was better than $> 44^\circ$C) [8]. More recently, we have found in canine sarcomas that improved oxygenation effects last at least 48 h post-heating and that they persist throughout a course of fractionated thermoradiotherapy, where hyperthermia is administered once a week (Thrall et al., unpublished data).

There is also evidence for lack of vascular shut-down during heating in the clinic. Probably the best data is published by Waterman et al., who measured changes in perfusion using thermal conduction methods [9]. Steady state temperatures up to 44°C were monitored without any thermal conduction-derived evidence for vascular damage during heating. In a later paper they observed an initial increase and then gradual declines in perfusion in four patients that were serially monitored over a course of thermoradiotherapy [10]. It is not known whether these gradual perfusion changes were associated with changes in oxygenation, but they were associated with tumour regression. These data argue that administration of hyperthermia prior to radiotherapy is not likely to cause transient hypoxia and radioresistance.

These clinical data, combined with the prior publications by Song's group in pre-clinical murine models, support the idea that vascular damage post-hyperthermia is not likely to occur following the types of thermal distributions that we typically encounter clinically [11–13]. We admit that one paper, using the C3H mammary carcinoma line, that does not demonstrate reoxygenation after heating [14], but the majority of the data, which includes that from human and canine patients is consistent with the hypothesis that hyperthermia as it is currently practiced, causes tumour reoxygenation. Thus, we have to conclude that hyperthermia mediated improvements in oxygenation are likely to play a major role in thermal radiosensitization. What will be important to determine in future studies is why this effect occurs after hyperthermia, as such knowledge may lead to further insights into how to

exploit the use of hyperthermia. As van der Zee et al. suggest, it must be either a result of reduced oxygen consumption or improvements in perfusion.

Van der Zee et al. claimed that we were advocating changing prescriptions to recommend lower temperatures during heating. This is a case of misunderstanding. In our recently published phase III trials, we required a minimum T_{90} value and then escalated dose mainly by changing the time of heating, as opposed to the temperatures achieved [15, 16]. Median temperatures achieved in these trials were in exactly the range reported for the chest wall recurrence meta-analysis reported by Vernon et al. [17]. In our trials, higher thermal doses, achieved primarily by prolonging the duration of heating or the number of hyperthermia fractions, yielded better outcomes. This does not necessarily equate with a scenario where actual temperature distributions are altered, however. It is our belief that the requirement that equipment be capable of increasing thermal dose by escalating temperatures beyond what is currently practiced may indeed lead to worse outcome as a consequence of hypoxia created by vascular damage and normal tissue complications (discussed below).

Van der Zee et al. also suggest that thermal dose escalation is inconsequential, based on prior publications that failed to show differences in tumour response for varying numbers of heat fractions when combined with radiotherapy [18, 19]. It is important to note that these prior studies were performed without prospective control of any aspect of the temperature distribution. Additionally, they did not exclude tumours that were not heatable, as defined with *a priori* criteria. Given the exponential relationship between temperature and cumulative thermal dose, it is likely that there was considerable overlap in total thermal dose between hyperthermia fractionation schemes and potential contamination of the study groups by tumours that were not heatable. These parameters were controlled in both of our recent trials [15, 16]. This is the most reasonable explanation for the lack of difference between the treatment arms.

We conclude this section in much the same way as van der Zee et al. We should not change our standards for thermal therapy without carefully controlled trials to verify that prospective escalation of thermal dose yields either superior or inferior outcome, compared with conventional treatment.

Why not apply hyperthermia more frequently than once or twice weekly?

Here van der Zee et al. agree with us that thermotolerance is not likely to be an important issue for the kinds of thermal distributions that we encounter. Our point here was that it is time to try a more frequent hyperthermia fractionation schedule that takes more advantage of thermal radiosensitization, since it is not affected by thermotolerance [20]. Further, if tumour oxygenation improvement is sustained better by more hyperthermia fractions, then this could lead to significant improvement in radioresponsiveness, compared to the more coarsely fractionated hyperthermia that is typically used.

Why not apply hyperthermia before or during radiotherapy?

Normal tissue complications

Our logic for recommending administration of hyperthermia before radiation is to take maximal advantage of heat induced reoxygenation. Van der Zee et al. argue that changing sequencing to emphasize application of hyperthermia before radiotherapy may increase normal tissue complications. This conclusion is based largely on pre-clinical rodent data,

where normal tissues (skin) were typically heated to an equal or greater extent than the tumour itself, via water bath heating. Furthermore, the tumour and skin received the same radiation doses. It is our belief that such data do not represent the clinical norm for two reasons. First, in many scenarios tumour is heated to a greater extent than surrounding normal tissues. More importantly, however, modern radiotherapy practice, which uses conformal and intensity modulated radiotherapy, can greatly minimize the radiation dose that surrounding normal tissue receives. As a result, it is highly unlikely that administration of hyperthermia before radiation will lead to increased normal tissue complications.

It is worth examining another body of data, however, that is directly relevant to this issue. The data we refer to are two pet animal clinical trials, published in the mid 1980s. The reason for considering these trials is that the heating devices used were the same as those used in the human clinic and the thermal distributions achieved were similar to human trials.

We conducted a phase III trial, comparing thermoradiotherapy to radiotherapy alone in 236 pets with spontaneous malignancies [21]. Hyperthermia was administered 15–30 min before radiotherapy. The incidence of late normal tissue complications was not greater in the combined group than in the radiotherapy alone group, with the following exception. In those animals in which burns were encountered, there was an increase in skin fibrosis [22]. Interestingly, the increase in thermal injuries was positively correlated with intra-tumoural maximum temperature ($p = 0.012$). Thus, this may have been the first data to suggest that control of thermal maxima in tumours needs to be exercised. Similar relationships were later reported by Kapp et al. [23] in human patients with superficial tumours.

Denman et al. [24] compared anti-tumour effects and normal tissue damage in canine patients randomized to be treated with three different schedules: radiotherapy alone, radiotherapy immediately followed by hyperthermia or hyperthermia administered 4–5 h after radiotherapy. The incidence of normal tissue complications was increased in both groups receiving hyperthermia, again associated with higher intra-tumoural temperature maxima. There was no difference in the severity or incidence of these injuries between the two sequences. This group also evaluated normal tissue injuries at 9 months after treatment by examining skin in the treatment field using quantitative histomorphometry. In both heat groups, there was mild evidence for more late effects, as indicated by a reduction in hair follicles. There was not a significant difference in vascular density between the heated groups and the group receiving radiotherapy alone. There was no difference in the severity of hair follicle loss between the two hyperthermia-radiotherapy sequences.

Based on these prior clinical data, we must conclude that one should use caution in elevating intra-tumoural temperature maxima beyond what is currently practiced, because of the risks for increasing normal tissue complications.

It is also important to note that there was significant improvement in response and local control duration for both hyperthermia treatment arms compared to radiotherapy alone, but no difference between the two hyperthermia treatment arms in the report by Denman et al. [24]. This is in contrast to the unpublished report quoted by van der Zee et al. in 87 patients where a non-significant improvement in response was reported when hyperthermia was administered after radiotherapy as compared with the opposite sequence [25].

Metastasis

Van der Zee et al. also suggest caution with respect to administering hyperthermia prior to radiotherapy, because of two reports (one pre-clinical and one clinical) suggesting that there is an increase in distant metastases induced by hyperthermia. One of the references was an unpublished thesis which was never subjected to peer-review and is not available for

examination. The other reference was a small randomized study in which hyperthermia was administered before radiotherapy vs radiotherapy alone for treatment of carcinoma of the cervix [26]. To be specific, the authors reported raw incidences of metastasis (1/23 in the radiotherapy arm vs 4/23 in the combined arm). There are significant problems with interpretation of this report. First, the authors excluded patients lost to follow-up from the analysis (two in each arm). Patients who died prior to 18 months follow-up and did not have evidence for metastasis (one in each arm) were treated as if they did not have distant metastases during the entire follow-up period. This creates a competing risk problem. The early occurrence of death or lost-to-follow-up completely eliminates or masks the possibility of having a metastasis later. In other words, a secondary type of event (death) competes with the primary event (metastasis). This is not a satisfactory approach unless one can safely assume that the competing risks behave independently from the event of interest. This is highly unlikely in this study since death and lost-to-follow-up are more likely associated with the incidence of distant metastasis. If the true information were known for the three missing patients in each arm, the proportions developing metastases might be very similar. Even considering the current data of 1/23 vs 4/23, the p-value is not significant, however ($p = 0.35$). An additional criticism is that with only 25 patients per treatment arm, the study was under-powered to predict if the difference seen would likely be significant in a larger population. Another technical problem with that paper was the use of an intra-cavitary heating device that did not yield adequate heating of the entire tumour volume. This could have contributed to alterations in metastasis.

It is important to point out also that in a randomized study of 65 head and neck cancer patients, treated with hyperthermia immediately prior to radiotherapy compared to radiotherapy alone, there was a significant difference in disease free and overall survival, compared with radiotherapy alone [27]. Metastasis data were not reported separately, but the disease-free survival analysis would have included such events. This report suffers the same weakness as the one reported by Sharma et al. [26], however. The small numbers of patients per group limits the power of the study.

Dewhirst et al. [28] examined local control vs development of metastasis in canine melanomas treated with thermoradiotherapy, where hyperthermia was administered 15–30 min prior to radiotherapy. Forty-two animals were randomized to receive radiotherapy alone or combined with hyperthermia. Survival analysis, to examine whether there was a difference in likelihood for metastasis, revealed no difference between the two arms. No animals were lost to follow-up, but there were two instances in which animals were euthanized because of local failure before there was evidence for distant metastasis. Both were in the group receiving thermoradiotherapy. This paper suffers from the same limitation as that of Sharma et al. [26], in that it is under-powered for this end-point. Nevertheless there was no hint that there was any difference between the arms for this end-point.

In a separate canine clinical trial where hyperthermia was administered 3–4 h after radiotherapy, higher normal tissue temperatures in the region surrounding the tumour were associated with lower incidence of distant metastases [29].

One has to also consider effects of systemic heating on the likelihood for metastasis formation. Kapp and Lawrence [30] reported that fevers associated with brachytherapy implants in cervix cancer patients were associated with higher risk for development of metastases. These same authors also observed an increase in osseous metastasis sites following whole body hyperthermia treatment of pet dogs with osteosarcoma [31]. In a canine soft tissue sarcoma trial that compared thermoradiotherapy regimens of local hyperthermia or combined with total body hyperthermia, the combination of local + whole body hyperthermia yielded shorter times to development of metastasis, but no difference

in the overall incidence [32]. Pre-clinical studies have been reported showing increased incidence of distant metastases following administration of whole body hyperthermia (41.8–42°C for 1 h) without any concomitant systemic chemotherapy [33, 34]. However, fever range whole body hyperthermia (40°C for 6 h) combined with a variety of cytotoxic drugs has been shown to decrease the incidence of metastases [35–37].

An important issue in interpreting time to metastasis is that failure to control local disease can indirectly influence metastatic rates [38, 39]. The cleanest data available to evaluate the influence of hyperthermia on metastatic rates comes from thermoradiotherapy studies in human soft tissue sarcomas. This is because combined modality therapy for extremity sarcomas has a very high local control rate, which therefore minimizes the competing risk issue. In a series of nearly 100 patients with soft tissue sarcomas treated pre-operatively with thermoradiotherapy, where hyperthermia was administered after radiation, the incidence of metastases was essentially equivalent to many prior publications in which radiotherapy only was used pre- or post-operatively [40].

There are two published studies conducted at the pre-clinical level examining whether thermoradiotherapy influences distant metastases. Hill and Denekamp [41] examined several schedules for thermoradiotherapy, including administration of hyperthermia (42.8°C, 60 min) 60 min prior, *immediately* prior or 1–2 h after radiotherapy using five different tumour lines that show propensity for pulmonary metastasis. One tumour line out of the five showed a significant increase in pulmonary metastases when hyperthermia was administered *immediately* before radiation. Baker et al. [42] performed a very similar series of experiments using the KHT tumour. The incidence of pulmonary metastases with a radiotherapy dose of 20 Gy was 100% and this was reduced to 50% with the addition of hyperthermia if it was given 1 h prior, 10 min prior or 1 h after radiotherapy. When hyperthermia was administered *simultaneously* with radiotherapy, the incidence of metastases was significantly increased, to 83%.

Based on this discussion, we conclude that there is no compelling evidence that administration of hyperthermia prior to radiotherapy has any deleterious consequences and carries the possibility of increasing oxygenation following treatment that could improve radiotherapy response for the radiotherapy fraction delivered on that day. In routine clinical application, it would not be practical to administer hyperthermia *immediately* prior to radiotherapy. In the aforementioned pet animal trial, it was administered 15–30 min prior to radiotherapy [28]. The two pre-clinical studies discussed above strongly suggest, if anything, that caution should be used if hyperthermia is to be administered simultaneously with radiotherapy.

There is evidence that elevation in systemic temperature might cause an increase in metastasis or alter sites of metastasis, but much more work needs to be done on this subject, using whole body hyperthermia regimens that fit modern fever range hyperthermia paradigms in combination with chemotherapy (i.e. fever range = 40°C for 6 h vs maximally tolerated whole body hyperthermia = 41.8°C for 1 h).

In conclusion

Our recommendations are somewhat different from those of van der Zee et al. They recommend that treatment regimens not be changed at this time and that every effort be extended to increase intra-tumoural temperatures as much as possible. We believe that we have shown credible data to suggest that increasing intra-tumoural temperatures excessively may in fact lead to increased likelihood for normal tissue complications and reduced

oxygenation. Neither of these consequences is desirable. We further believe that there is no strong evidence for concluding that administering hyperthermia prior to radiotherapy carries any increased risk for metastases.

Now is the time for those in the field of hyperthermia to be bold and think outside the traditional biological barriers that were established well over two decades ago. We must also adhere to the principles of evidence-based medicine and design clinical trials that build upon significant findings from prior trials. Status quo will not advance the field of hyperthermia. The practice of radiotherapy has also changed dramatically in this period and our ability to monitor and evaluate the physiologic changes occurring in tumours has greatly improved. If we are to truly show that hyperthermia is a credible modality to be combined with other forms of therapy, we need to conduct credible clinical trials to test some of these new paradigms. Such trials should be conducted in a manner that objective measures of parameters relevant to the issues raised by this discussion are ollected prospectively.

Mark W. Dewhirst, Donald Thrall, Zeljko Vujaskovic,
Daohai Yu, Ellen Jones, & Peter Corry

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IN REPLY TO VAN DER ZEE ET AL.

Hyperthermia dose and schedule: No evidence yet for changing treatment design

We agree with the majority of what is mentioned by van der Zee et al. in their letter to the editor as well as the response from Dewhirst et al. However, we would like to make the following additional observations. We feel that there has been misunderstanding of the way in which we view the 'mild temperature hyperthermia' issue. This may differ slightly from the views of the authors of the other papers mentioned by van der Zee et al. Foremost is the fact that we are not suggesting to try and heat less than what is being done, or can be done, with currently available hyperthermia devices. It must be emphasized that, regardless of the heating goal, there is a varied and complex temperature gradient that occurs in living tumour tissue in response to heat. Our entire focus has been to recognize the reality that a large portion (at least enough to easily repopulate the tumour) of most tumours is not being heated at cytotoxic temperatures with conventional heating techniques. This is quite evident by reviewing the thermometry data available from almost any of the clinical trials performed to date. Therefore, the effects of sub-lethal heating of tumour on subsequent radiation or chemotherapy response are arguably the most important to the treatment outcome.

In our work we have tried to point out that our observations, along with clinical observations from the Duke University group and others, indicate that increased tumour oxygenation is one of the major responses when tumour is exposed to mild-to-moderate heating. Therefore, heat-induced oxygenation of the tumour is likely involved in the positive clinical responses to thermoradiotherapy noted by van der Zee et al. We fully recognize inhibition of DNA repair as another factor that affects tumour response to thermoradiotherapy. However, since the time gap between irradiation and heating was 30–60 min or longer in most clinical situations and most DNA double strand breaks may be repaired by this time, the true contribution of these effects to the clinical results to date must be clarified. However, the kinetics of increased oxygenation may have a much more favourable profile for impacting the effects of subsequent rounds of radiation therapy. As we have discussed in our review article [1], we and others have observed numerous instances where tumour oxygenation did not return to control level until 1–3 days after heating in some tumour models. In addition, in the recent report from our laboratory referred to by van der Zee et al. [2] we found that the effects of carbogen breathing

on tumour radiation sensitivity significantly increased immediately after heating at 41.5°C as well as at 24 h after heating compared to carbogen breathing alone. It is hard to conceive of a reason other than blood flow or perfusion improvement that would explain such a significant increase in the radiosensitization observed with carbogen breathing after local heating of the tumour. As an important aside, in view of this data we would advocate that carbogen breathing should be seriously considered for inclusion with all thermoradiotherapy clinical applications. A further noted study related to these issues comes from Waterman et al. [3] where human tumour blood flow was assessed before, during and after microwave heating. In that study, increases in tumour blood flow at temperatures as high as 45°C were recorded with no apparent vascular shutdown occurring. This study serves as a reminder that less tumour destruction may occur in the human situation than would be predicted on thermometry and knowledge of rodent tumour heat sensitivity. Our views are further strengthened by these observations, i.e. there may be significant, yet limited, areas of tumour being killed by conventional hyperthermia in the clinic but there are as many or more discrete volumes of the tumour that experience increased oxygenation via increased blood flow and possibly decreased oxygen consumption. Regardless, since in the ESHO study tumours were generally heated twice a week, the time interval between heating and radiation was most likely between 1–3 days, with the possible exception being weekends off. We surmise that whenever the interval between heating and radiation was shorter than 3 days, heat-induced oxygenation of the tumour likely played a significant role in increasing tumour cell killing by radiation.

An interesting addition to this debate that helps to illustrate our understanding of the complex and heterogeneous nature of solid tumour physiology and reaction to thermal stress comes from recent work in our laboratory. We are observing that in tumours heated by thermal ablation techniques there are regions that are exposed to sub-lethal temperatures and oxygenation is increased (unpublished data). Therefore, even in situations where the goal is to heat to the maximum possible (as it is with conventional heating as van der Zee et al. suggests) there could be significant sub-lethal heating that will affect the response to subsequent radiation or chemotherapy (due to the potential of increased drug delivery). Therefore, we cannot emphasize enough the need for detailed studies of the patterns of heat induced changes in blood flow and oxygenation in the tumour and the critical role that treatment sequencing will play in bettering the clinical outcomes in future thermoradiotherapy trials. We hope that the discussion over these issues will only help to increase our collective knowledge about the tumour response to a range of heating temperatures and help to explain the clinical results that have already been achieved. With further detailed study it appears reasonable to assume that there will finally be valid reason(s) to change currently accepted heating practices, if not in terms of temperature, at least in terms of frequency, addition of adjuvants such as carbogen breathing and more precise sequencing with radiotherapy.

Robert J. Griffin, & Chang W. Song
University of Minnesota Medical School, Radiation Biology Section,
Department of Therapeutic Radiology

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