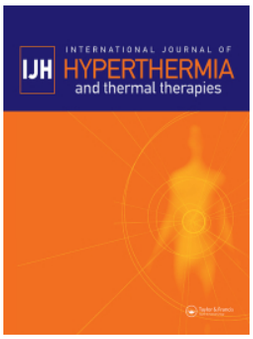

International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

Prospective thermal dosimetry: The key to hyperthermia's future

Ellen Jones, Donald Thrall, Mark W. Dewhirst & Zeljko Vujaskovic

To cite this article: Ellen Jones, Donald Thrall, Mark W. Dewhirst & Zeljko Vujaskovic (2006) Prospective thermal dosimetry: The key to hyperthermia's future, International Journal of Hyperthermia, 22:3, 247-253, DOI: 10.1080/02656730600765072

To link to this article: https://doi.org/10.1080/02656730600765072

Int. J. Hyperthermia, May 2006; 22(3): 247–253

Taylor & Francis
Taylor & Francis Group

Prospective thermal dosimetry: The key to hyperthermia's future

ELLEN JONES[1], DONALD THRALL[2], MARK W. DEWHIRST[1], & ZELJKO VUJASKOVIC[1]

[1]*Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA and* [2]*APR Department, School of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA*

(Received 12 January 2006; accepted 22 April 2006)

Abstract

Purpose: This review summarizes recent results from two randomized trials testing the complete response rate and local control benefits for the addition of hyperthermia to external beam radiation.
Methods: In both series, there was a statistically significant benefit to adjuvant hyperthermia.
Results: The establishment of a standardized nomenclature for clinical hyperthermia prescription will help to facilitate the broader usage of hyperthermia.
Conclusions: Carefully conducted phase III trials with rigorous quality assurance must employ prospective thermal dosimetry to validate the role of hyperthermia in multi-modality therapy.

Keywords: *Thermal dosimetry, thermal dose response, CEM 43°C T90, thermal radiosensitization*

Introduction

Hyperthermia, the elevation of tumour temperature to a supraphysiologic level in the range of 40–44°C, is a well-established radiosensitizer. The predominant molecular target appears to be protein [1]. For many cells and tissues (both tumour and normal), the heat of inactivation for cell killing is in the range of that necessary for protein denaturation (130–170 kcal mole^{-1}). Additional evidence for proteins as the primary target for cell killing is the importance of heat shock proteins (HSPs) in protecting cells from thermal damage.

The rationale for combining hyperthermia with radiation is multi-fold. Mechanisms of action are complimentary to the effects of radiation with regard to DNA damage repair [2], cell cycle sensitivity [3] and hypoxia [4]. Hyperthermia causes direct cytotoxicity,

Correspondence: Ellen Jones, MD, PhD, Department of Radiation Oncology, Duke University Medical Center, Durham, NC 27710, USA. E-mail: Jones198@mc.duke.edu

ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.1080/02656730600765072

particularly to cells which are acidotic [5] and nutrient deprived [4]. In addition, hyperthermia has effects on tumour blood flow and oxygenation which may enhance tumour radiation response [6].

Pre-clinical studies have established that hyperthermic radiosensitization depends on temperature achieved and duration of heating [7]. Hyperthermia combined with radiotherapy has improved clinical response, local control and survival in numerous phase II studies and several randomized trials for patients with breast, cervix, head and neck cancers, melanoma and glioblastoma multiforme [8–15]. Despite positive phase III trials, application of hyperthermia remains limited. This may partially relate to the lack of rigorous thermal dosimetric data. The basic premise underlying the need for thermal dosimetry is the ability to write a verifiable prescription for hyperthermia. As in any form of therapy, a sound dosimetric basis leads to unambiguous treatment, data reporting and quality assurance [16].

These studies were designed to test the clinical value of hyperthermia based on dosimetric principles established in the preclinical setting [17] and retrospective analysis of human phase II trials [18]. Quality of treatment was assured using strict application of pre-defined thermal dose criteria as a 'test treatment' to prospectively determine whether thermal dose prescription could be achieved.

Materials and methods: Thermal dosimetry

It is well established that the rate of cell killing is exponential and dependent on the temperature achieved. Roughly, over the clinically relevant range of temperatures (39.5–50°C), the rate of cell killing doubles for every degree increase in temperature. If thermotolerance is present at temperatures below 43°C, the rate of cell killing changes by a factor of four for every degree decrease in temperature. This well characterized relationship between temperature and rate of cell killing facilitated the development of a method for converting any time–temperature history into an equivalent number of minutes at a standard temperature, such as 43°C, commonly referred to as CEM 43°C. This dosimetric concept was accepted only slowly, largely because of early concerns about factors that could alter the rate of cell killing (such as thermotolerance). However, the value of this method of dosimetry for prediction of tumour response and duration of local control has now been established in a number of clinical trials and early concerns about the validity of the concept have largely been dispelled.

One disservice that the CEM 43°C concept did for the hyperthermia community, however, was to foster the view that 43°C was a treatment goal and that inability to achieve this temperature during treatment meant that the treatment had failed. Evaluation of many published clinical series state that the target treatment temperature was 43°C and the primary design goal for many hyperthermia devices has been to achieve this temperature. In fact, temperatures during hyperthermia are never spatially uniform and frequently range between 39–50°C during a single treatment. Some small zone in a tumour may reach the target of 43°C, but most temperatures are lower. Thus, a prescription based on a single target temperature carries little therapeutic meaning and cannot be realistically achieved in the vast majority of patients.

Alternatively, it has been shown in several clinical series that temperatures that describe the lower end of the temperature distribution, such as the minimum or T_{90}, are usually well below 43°C, yet are correlated with therapeutic effects when combined with radiation. The advantage of the CEM 43°C concept is that any temperature measured during treatment can be converted to CEM 43°C. This allows thermal histories in different parts of the tumour as

well as between patients to be made. The conversion of time–temperature histories to CEM 43°C for the convenience of hyperthermia dose standardization does not in any way imply that 43°C is a 'target temperature' for hyperthermia.

From these two approaches, terminology evolved that converted percentile descriptors of multi-point thermal data, such as the T_{90} or T_{min}, to an equivalent number of minutes at a standard temperature. In the most common form, this has resulted in the reporting of data as CEM 43°CT_{90} or CEM 43°CT_{min}. The nomenclature refers to cumulative equivalent minutes at 43°C at the T_{index} value (e.g. T_{90} or T_{min}). In practice this is usually accomplished by calculating the average T_{90} or T_{min} over each minute of a treatment, converting that data to an equivalent number of minutes at 43°C and summing up those data. Some investigators have also summed this type of data over several treatments.

Hyperthermia improves complete response rate and local control in superficial human tumours

This trial was designed to test whether a thermal dose of >10 min CEM 43°CT_{90} results in improved complete response and duration of local control compared to a thermal dose of ≤1 CEM 43°CT_{90}. Patients with superficial tumours (≤3 cm depth) received a test dose of hyperthermia ≤1 CEM 43°CT_{90}. Tumours deemed heatable were randomized to additional hyperthermia (HT) vs no further hyperthermia (no HT). Hyperthermia was given using microwave spiral strip applicators operating at 433 MHz.

One hundred and twenty-two patients were enrolled, 109 (89%) were deemed heatable and were randomized. The complete response rate in the HT arm was 66.1% and in the no HT arm 42.3%. The odds ratio for complete response was 2.7 (95% CI [1.2–5.8], $p = 0.02$). There was further a significant improvement in duration of local control (Figure 1). Previously irradiated patients had the greatest incremental gain in complete response, four of 17 patients (23.5%) in the no HT arm vs 15 of 22 patients (68.2%) in the HT arm. No overall survival benefit was seen. Adjuvant hyperthermia with a thermal dose >10 CEM 43°CT_{90} confers a significant local control benefit in patients with superficial tumours receiving radiation therapy.

Thermal dose and duration of local control in canine sarcomas

In a series of spontaneous canine sarcoma patients (all *de novo* tumours), the prospective delivery of higher thermal dose was associated with longer tumour control duration. One hundred and twenty-two dogs with a heatable soft tissue sarcoma were randomized to receive a low (2–5 CEM 43°CT_{90}) or high (20–50 CEM 43°CT_{90}) thermal dose in combination with radiotherapy. Most dogs (90%) received four-to-six hyperthermia treatments over 5 weeks.

In the primary analysis, median (95% CI) duration of local control in the low-dose group was 1.2 (0.7–2.1) years vs 1.9 (1.4–3.2) years in the high-dose group (log-rank $p = 0.28$). The probability (95% CI) of tumour control at 1 year in the low-dose vs high-dose groups was 0.57 (0.43–0.70) vs 0.74 (0.62–0.86), respectively. Using multi-variable procedure, thermal dose group ($p = 0.023$), total duration of heating ($p = 0.008$), tumour volume ($p = 0.041$) and tumour grade ($p = 0.027$) were significantly related to duration of local tumour control. When correcting for volume, grade and duration of heating, dogs in the low-dose group were 2.3 times as likely to experience local failure.

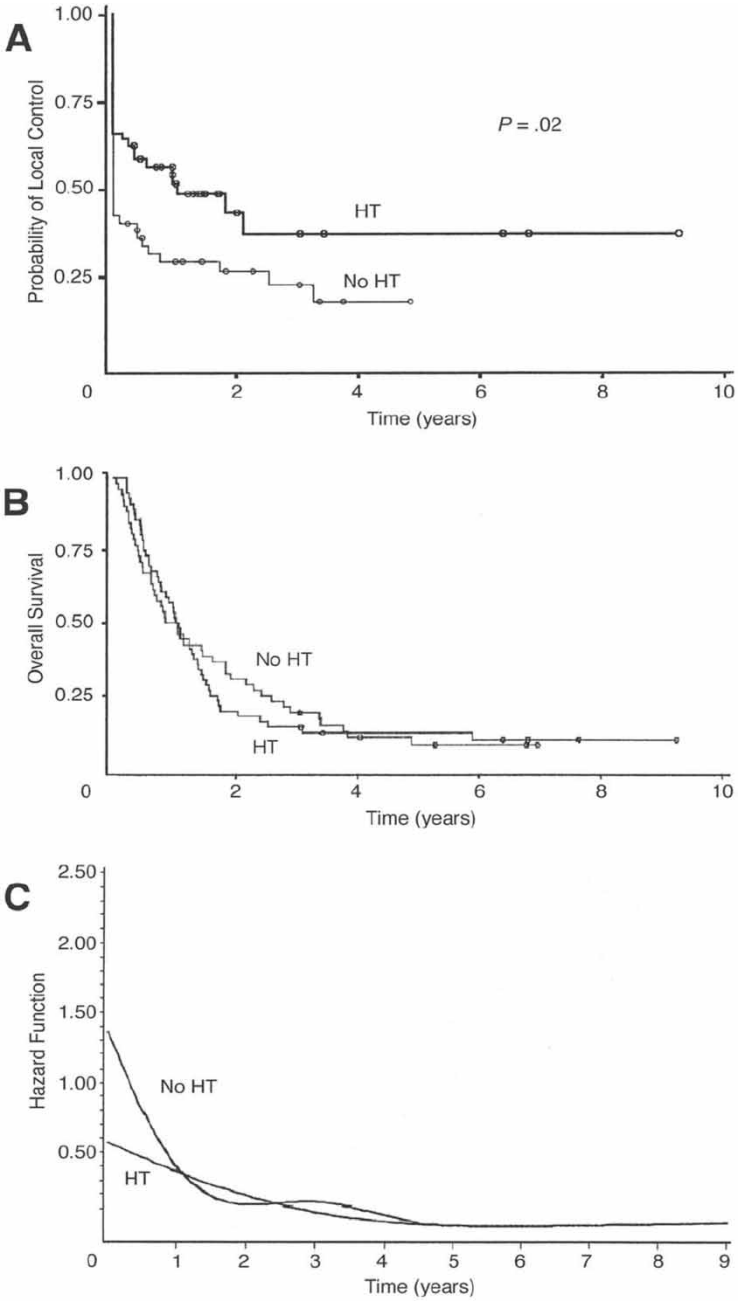

Figure 1. (*a*) Time to local failure, all patients, log-rank $p = 0.02$. The primary difference between the two arms occurred at the beginning of the study, corresponding to a significant difference in the complete remission rates in the two arms. (*b*) Overall survival, all patients, log-rank $p = 0.84$. (*c*) Hazard function of time to local failure by arm, all patients, log-rank $p = 0.02$. Hazard means the risk of having a local failure. Note that the primary difference in the hazard functions between the two arms seemed to have occurred within the first 6 months, likely due to the difference in the complete remission rates in the two arms. The competing risks, including death, were assumed to be independent of this outcome in the two arms. HT, hyperthermia. Figure reproduced from Jones et al., J Clin Oncol 23:3079–3085, 2005 [19], with permission.

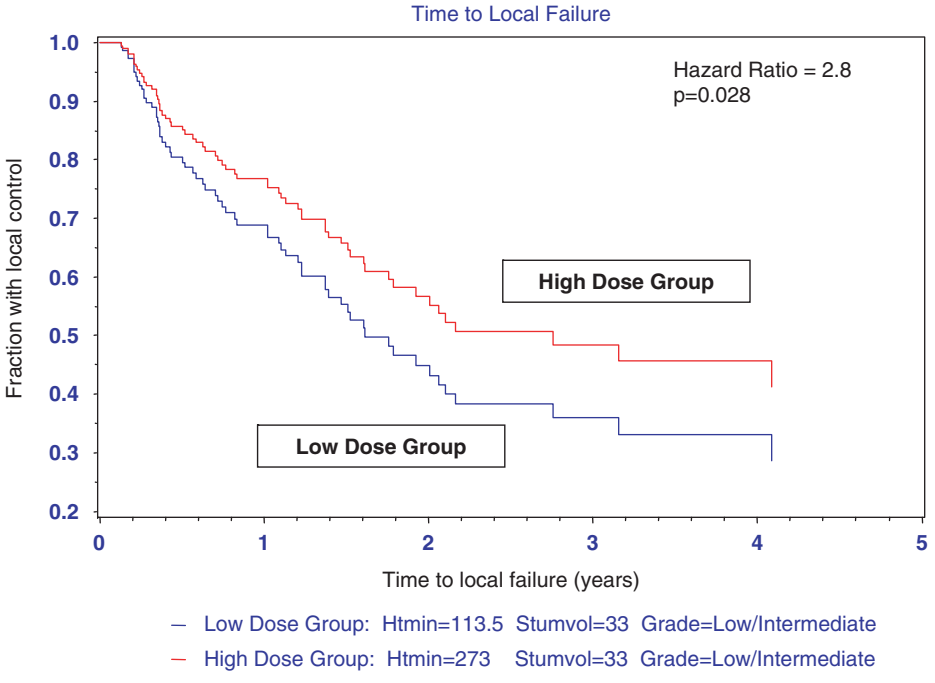

Figure 2. Estimated survival distribution functions of time to local failure for a 'typical' dog in the low and high thermal dose groups from the Cox proportional hazards model. There is a significant association between thermal dose group and time to local failure after controlling for total duration of heating, tumour volume and tumour grade (hazard ratio of low vs high, 2.28; 95% CI 1.12–4.64; $p = 0.023$). Duration of heating and tumour volume values used in the estimation of survival functions were median values for the respective group and overall, respectively. Ht_{min}, total duration of heat treatment; median duration of heating in the thermal dose group was used in the plot. $Stum_{vol}$, median tumour volume over all dogs in trial. Figure adapted from Thrall et al., Clin Cancer Res 11:5206–5214, 2005 [20].

Thermal dose is directly related to local control duration in irradiated canine sarcomas (Figure 2). Longer heating being associated with shorter local tumour control was unexpected. However, the effect of thermal dose on tumour control was stronger than for heating duration. The heating duration effect is possibly mediated through deleterious effects on tumour oxygenation. These results are the first to show the value of prospectively controlled thermal dose in achieving local tumour control with thermoradiotherapy and they establish a paradigm for prescribing thermoradiotherapy and writing a thermal prescription.

Summary and future directions

One lives in a world of evidence-based medicine. One simply cannot ignore the evidence that prospectively defined and delivered thermal dose, quantified as CEM 43°CT_{90} and based on tumour temperature measurements, is related to clinical outcome; this study has shown this both in canine and in human tumours. One does not know if a better thermal descriptor exists or whether there is a universally applicable thermal descriptor.

However, the studies reviewed here demonstrate a clear correlation of the thermal descriptor CEM 43°CT_{90} to outcome. Efforts to refine three-dimensional thermal dose distributions with non-invasive MR-based thermometry may enhance the progress that has been made with regard to characterizing thermal dose. Ultimately, these efforts will optimize the clinical applications of hyperthermia.

Acknowledgements

This work was supported by a grant from the NIH/NCI CA42745. The authors appreciate the assistance of Vlayka Liotcheva in data management. This work was presented at the European Society for Hyperthermic Oncology in Graz, Austria, May 2005.

References

1. Lepock JR. Cellular effects of hyperthermia: Relevance to the minimum dose for thermal damage. Int J Hyperthermia 2003;19:252–266.
2. Mivechi NF, Dewey WC. DNA polymerase alpha and beta activities during the cell cycle and their role in heat radiosensitization in Chinese hamster ovary cells. Radiat Res 1985;103:337–350.
3. Armour EP, McEachern D, Wang Z, Corry PM, Martinez A. Sensitivity of human cells to mild hyperthermia. Cancer Res 1993;53:2740–2744.
4. Koutcher JA, Barnett D, Kornblith AB, Cowburn D, Brady TJ, Gerweck LE. Relationship of changes in pH and energy status to hypoxic cell fraction and hyperthermia sensitivity. Int J Radiat Oncol Biol Phys 1990;18:1429–1435.
5. Engin K, Leeper D, Thistlethwaite A, Tupchong L, McFarlane JD. Tumor extracellular pH as a prognostic factor in thermoradiotherapy. Int J Radiat Oncol Biol Phys 1994;29:125–132.
6. Song CW. Effect of local hyperthermia on blood flow and microenvironment: A review. Cancer Res 1984;44:4721s–4730s.
7. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia 2003;19:267–294.
8. Vernon CC, Hand JW, Field SB, Machin D, Whaley JB, van der Zee J, van Putten WL, van Rhoon GC, van Dijk JD, Gonzadez Gonzalez D, Liu FF, Goodman P, Sherar M. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: Results from five randomized controlled trials. International Collaborative Hyperthermia Group. Int J Radiat Oncol Biol Phys 1996;35:731–744.
9. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, Arcangeli G, Dahl O, Mella O, Bentzen SM. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. Lancet 1995;345:540–543.
10. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys 1994;28:163–169.
11. Datta NR, Bose AK, Kapoor HK, Gupta S. Head and neck cancers: Results of thermoradiotherapy versus radiotherapy. Int J Hyperthermia 1990;6:479–486.
12. van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000;355:1119–1125.
13. Harima Y, Nagata K, Harima K, Ostapenko VV, Tanaka Y, Sawada S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int J Hyperthermia 2001;17:97–105.
14. Sharma S, Sandhu AP, Patel FD, Ghoshal S, Gupta BD, Yadev NS. Side-effects of local hyperthermia: Results of a prospectively randomized clinical study. Int J Hyperthermia 1990;6:279–285.
15. Sneed PK, Stauffer PR, McDermott MW, Diederich CJ, Lamborn KR, Prados MD, Chang S, Weaver KA, Spry L, Malec MK, Lamb SA, Voss B, Davies RL, Wara WM, Larson DA, Philips TL, Gutin PH. Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/− hyperthermia for glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1998;40:287–295.

16. Dewhirst MW, Griffin TW, Smith AR, Parker RG, Hanks GE, Brady LW. Intersociety Council on Radiation Oncology essay on the introduction of new medical treatments into practice. J Natl Cancer Inst 1993;85:951–957.
17. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys 1984;10:787–800.
18. Oleson JR, Samulski TV, Leopold KA, Clegg ST, Dewhirst MW, Dodge RK, George SL. Sensitivity of hyperthermia trial outcomes to temperature and time: Implications for thermal goals of treatment. Int J Radiat Oncol Biol Phys 1993;25:289–297.
19. Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vajaskovic Z, Yu D, Sanders LC, Dewhirst MW. Randomized trial of hyperthermia and radiation for superficial tumors. J Clin Oncol 2005;23:3079–3085.
20. Thrall DE, LaRue SM, Yu D, Sanders L, Case B, Rosner G, Azuma C, Poulson J, Pruitt AF, Stanley W, Hauck ML, Williams L, Hess P, Dewhirst MW. Thermal dose is related to duration of local control in canine sarcomas treated with thermoradiotherapy. Clin Cancer Res 2005;11:5206–5214.