Hyperthermia as an adjuvant to radiation therapy of recurrent or metastatic malignant melanoma. A multicentre randomized trial by the European Society for Hyperthermic Oncology

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The ESHO protocol 3-85 is a multicentre randomized trial investigating the value of hyperthermia as an adjuvant to radiotherapy in treatment of malignant melanoma. A total of 134 metastatic or recurrent malignant melanoma lesions in 70 patients were randomized to receive radiotherapy alone (3 fractions in 8 days) or each fraction followed by hyperthermia (aimed for 43°C for 60 min). Radiation was given with high voltage photons or electrons. Tumours were stratified according to institution and size (above or below 4 cm) and randomly assigned to a total radiation dose of either 24 or 27 Gy to be given with or without hyperthermia. The endpoint was persistent complete response in the treated area. A number of 128 tumours in 68 patients were evaluable, with an observation time between 3 and 72 months. Sixty-five tumours were randomized to radiation alone and 63 to radiation + heat. Sixty received 24 Gy and 68 tumours received 27 Gy, respectively. Size was < 4 cm in 81 and > 4 cm in 47 tumours. Overall the 2-year actuarial local tumour control was 37%. Univariate analysis showed prognostic influence of hyperthermia (rad alone 28% versus rad + heat 46%, \( p = 0.008 \)) and radiation dose (24 Gy 25% versus 27 Gy 56%, \( p = 0.02 \)), but not of tumour size (small 42% versus large 29%, \( p = 0.21 \)). A Cox multivariate regression analysis showed the most important prognostic parameters to be: hyperthermia (odds ratio: 1.73 (1.07-2.78), \( p = 0.02 \)), tumour size (odds ratio: 0.91 (0.85-0.99), \( p = 0.05 \)) and radiation dose (odds ratio: 1.17 (1.01-1.36), \( p = 0.05 \)). Analysis of the heating quality showed a significant relationship between the extent of heating and local tumour response. Addition of heat did not significantly increase the acute or late radiation reactions. The overall 5-year survival rate of the patients was 19%, but 38% in patients if all known disease was controlled, compared to 8% in the patients with persistent active disease.

Key words: Malignant melanoma, hyperthermia, radiotherapy, randomized multicentre trial, local control, survival, thermometry, quality assurance

1. Introduction

The use of heat as a method to improve radiation response in tumours was clinically introduced in 1910 by C. Müller who described the potential of using local diathermia as an adjuvant to radiotherapy (Müller 1910). For many years thereafter sporadic reports enthusiastically demonstrated a potential improvement
of radiotherapy but it was not until the mid-70’s that the concept was explored more scientifically. This subsequently led to numerous uncontrolled studies which strongly suggested that adjuvant hyperthermia may increase the probability of controlling tumours by radiotherapy (Arcangeli et al. 1987, Meyer et al. 1989, Overgaard 1989).

The biological rationale for combining hyperthermia with radiation has been well explored and a detailed discussion of the rationale and strategies to apply heat and radiation has been given elsewhere (Overgaard 1989, 1990, Overgaard and Bach Andersen 1995).

A major problem with clinical hyperthermia has been the ability to provide a homogeneous heating to a given tumour area and despite intense research in this area, the problem is far from solved. Nevertheless there has been an abundant clinical experience in uncontrolled studies where combined heat and radiation has been applied and in general they have all pointed towards a significant benefit of combining heat with radiation relative to radiation alone (Hofman et al. 1989, Overgaard 1989). Furthermore, these early clinical studies have indicated that a significant improvement in local control could be obtained without increasing normal tissue morbidity if either a relatively long interval between the two modalities was allowed for or if the tumours were heated (semi)selectively. From the early studies it appeared that especially three tumour sites have been the subject of combined heat and radiation therapy, namely advanced neck nodes, recurrent or advanced breast tumours, and malignant melanoma (Kapp 1986, Overgaard 1987, 1990, Arcangeli et al. 1988, Meyer et al. 1989, Ben-Yosef and Kapp 1993, Dewhirst et al. 1993). Part of the reason for this was the superficial nature of these tumours, but accumulating evidence from early clinical trials indicates that a significant improvement in local control was likely to be obtained without increasing normal tissue morbidity. Thus dose-response analyses of available data indicated a thermal enhancement ratio in the order of 1.5 (Overgaard 1989).

The fact that malignant melanoma has been found to respond well to radiotherapy given in large doses per fraction (Overgaard 1986), and that the response apparently can be significantly improved by adding hyperthermia (Overgaard 1981, 1995, Kim et al. 1982, Gonzalez Gonzalez et al. 1986, Arcangeli et al. 1987, Emami et al. 1988, Overgaard and Bentzen 1990, Shidnia et al. 1990, Engin et al. 1992), makes this tumour type one of the most suitable clinical models for investigations of the interaction between radiotherapy and hyperthermia. The few fractions which can be spaced with relatively long intervals (several days) apparently without influencing the tumour control probability (Bentzen et al. 1989) allow treatment with hyperthermia in association with each radiation fraction without having the treatment compromised by the problems of thermotolerance (Overgaard and Nielsen 1983, Sapareto 1987). Thus a pilot study clearly indicated the feasibility of such strategy and several studies have indicated that a 3-fraction radiation schedule using a dose of 8–9 Gy per fraction appears to be one of the most suitable radiotherapy schemes for this disease (Overgaard and Overgaard 1987).

On this basis the European Society for Hyperthermic Oncology in January 1986 initiated a multicentre randomized clinical trial (ESHO protocol 3-85) with the aim to assess the efficacy of local hyperthermia given as an adjuvant to radiotherapy in the treatment of advanced malignant melanoma lesions, to evaluate the tumour response and local control probability, assess early and late tolerance in normal tissues, and evaluate the feasibility of various heating techniques (Overgaard 1987).

A report of the trial focusing on the local control data has previously been
published (Overgaard et al. 1995a), but the present study contains a more detailed analysis of parameters related to the outcome of the study, describes the quality of the heat treatment and the impact of local control on survival.

2. Patients and methods

2.1. Patients

This multicentre randomized trial included patients with advanced, recurrent, or metastatic lesions of non-lentiginous malignant melanoma who were estimated to be candidates for radiotherapy. The patients should have a life-expectancy > 3 months and should not be subjected to other cancer therapy (especially chemotherapy) concurrently with the protocolized treatment. The treated areas should not previously have been treated with radiotherapy. All lesions included should be considered feasible for heating with the available equipment.

The protocol has been performed according to the guidelines laid down in the Helsinki Declaration 11. In addition, the protocol was adapted and approved by all relevant national or local ethical committees.

2.2. Trial design

Since patients with this disease may frequently have multiple lesions and the treatment applied was local, the protocol was designed to allow inclusion of multiple lesions in the same patients. Thus randomization was performed based on individual lesions rather than on patients.

Tumours were stratified according to institution and size (≤ 4 cm versus > 4 cm in largest diameter) and randomized to one of the following schedules:

(a) Radiotherapy alone (24–27 Gy tumour dose to gross tumour). Radiation was randomized to be given in 3 fractions of either 8 or 9 Gy with 4 days' interval between fractions (i.e. Monday–Friday–Tuesday or Thursday–Monday–Friday); or

(b) Radiation as above (randomized to either 8 or 9 Gy per fraction) with each fraction followed within 30 min by hyperthermia. The heat session should aim for a minimal tumour treatment temperature of 43-0°C in 60 min.

2.3. Randomization

Randomization was performed centrally by telephone or fax. In patients with multiple tumours, each tumour was given a number prior to randomization. The same radiation dose was given to both lesions and if the first was randomized to radiation, the second would be given combined treatment or vice versa. Patients with 3 tumours were considered as patients with 2 plus 1 tumour, etc.

2.4. Treatment

Radiation was applied with either electrons or high-voltage photons through one or multiple portals. Radiation therapy doses were as specified in ICRU report 29, (1978).

Hyperthermia was applied with microwave or radiofrequency equipment. There was no limitations to the equipment used except that it should be likely to provide a tumour temperature of 43-0°C. Active skin cooling was allowed. The heat treatment should be applied after each of the radiation fractions and should be started within
30 min. Efforts should be made to avoid heating of normal tissue or to apply appropriate skin cooling. Hyperthermia and thermometry (with multiple measurement points in both tumour and normal tissue) were performed and recorded in accordance with the ESHO quality assurance guidelines previously published (Hand et al. 1989). In addition to the actual temperatures and times recorded, these values were also calculated as equivalent minutes at 43°C (Field and Morris 1983, Dewey 1994).

2.5 Follow-up and evaluation

Patients were seen 2 and 4 weeks after completion of therapy, then monthly for the next 3 months. At each follow-up normal tissue reaction and tumour response were recorded. The end-point of the study was complete response (at 3 months) and persistent local control, acute and late normal tissue damage. Tumour response was defined according to WHO (Miller et al. 1981). Early and late radiation damage was recorded as previously described (Overgaard et al. 1995a). All time estimates used the date of randomization as initial value.

2.6. Statistical considerations

The known dose-response relationship for both radiation alone and combined radiation and hyperthermia found in malignant melanoma suggested that after addition of hyperthermia a 30% improvement in local control may be expected. If the true frequency of tumour control is changed by 30% (from 50 to 80%) the likelihood that a significant difference is observed \( p < 0.05 \) is >90% when 120 evaluable lesions are included. The trial was therefore designed to be closed after 120 evaluable lesions had reached the 3-month follow-up.

The primary endpoint was persistent local control, which was estimated by Kaplan-Meier analysis using the Mantel-Cox test for comparison. Frequencies were compared by chi-square test. Multivariate analyses of local control was performed by the Cox proportional hazards model using the BMDP 2L programme. Multivariate analysis of complete response at 3 months was performed by logistic regression analysis using the BMDP LR programme. The treatment effect was evaluated using 'the intention to treat' principle and evaluable lesions were included in the randomization group irrespectively of whether or not they had completed the planned treatment. Analysis of thermometry data and other non-normal distributed comparison was performed by the Spearman rank correlation test, and comparison of paired data analysed by McNemar's test. In addition to the analysis of the randomized tumours the influence on patient survival of local tumour response and other prognostic parameters were investigated.

3. Results

3.1. Patients and tumours

One hundred and thirty-four lesions in 70 patients were randomized between January 1986 and May 1992. Among these 128 lesions in 68 patients were evaluable for analysis. One patient had two lesions removed by surgery before follow-up (one radiation alone, one combined treatment). One patient refused any participation and follow-up after randomization (one lesion randomized to radiation alone), and three lesions were never evaluated due to death before first follow-up (two combined treatment, one radiation alone).
Table 1. Characteristics of 128 evaluable tumours.

<table>
<thead>
<tr>
<th></th>
<th>Rad alone</th>
<th>Rad + Heat</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumours</td>
<td>65</td>
<td>63</td>
</tr>
</tbody>
</table>
| Tumour size
  median (range)       | 3 (1–14)  | 3 (1–13)   |
  \(\leq 4\) cm         | 41        | 40         |
  > 4 cm                 | 24        | 23         |
| Depth under skin (cm)
  median (range)       | 2 (1–7)   | 2 (1–7)    |
| Radiation
  24 Gy                 | 31        | 29         |
  27 Gy                 | 34        | 34         |
| Number of tumours in pt.
  single median (range) | 15        | 22         |
| Site
  lymph node           | 19        | 19         |
  skin/subcutis         | 49        | 44         |
| Type
  local recurrence     | 9         | 7          |
  metastasis            | 56        | 56         |
| Months to recurrence
  median (range)       | 14 (0–113)| 13 (0–203)|
| Observation time
  median (range)       | 7 (3–65)  | 9 (3–73)   |
| Female sex             | 26        | 26         |
| Age (years)
  median (range)       | 57 (32–88)| 59 (19–88)|

Table 2. Initial tumour response in 128 evaluable tumours.

<table>
<thead>
<tr>
<th></th>
<th>Rad alone</th>
<th>Rad + Heat</th>
<th>All tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response (NR)</td>
<td>28</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>37</td>
<td>27</td>
<td>32</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>35†</td>
<td>62†</td>
<td>48</td>
</tr>
<tr>
<td>Response rate (CR + PR)</td>
<td>72†</td>
<td>89†</td>
<td>80</td>
</tr>
</tbody>
</table>

†\(p = 0.003\); †\(p = 0.02\).

Of the 68 patients, 33 were females. Thirty-seven patients had a single tumour whereas 31 patients had multiple (2 to 7) treated lesions. The median age was 58 years ranging from 19 to 88 years. The median observation time were 11 months (range: 3–73 months).

The tumour characteristics are given in Table 1 showing the two treatment groups to be comparable with regard to tumour volume, radiation dose, numbers and site of tumours, months to recurrence of the lesion in question, and observation time. Also the sex and age of the patients showed no difference.

3.2. Tumour response

Overall the treatment yielded a high response rate (Table 2) and resulted in a significant palliative effect in most patients, irrespectively of the treatment arm. One hundred and three (80%) of the tumours obtained a complete or partial response.
Table 3. Univariate analysis of initial complete response and 2-year actuarial local control value as a function of treatment or stratification group.

<table>
<thead>
<tr>
<th>Stratification group</th>
<th>No. tumours</th>
<th>CR rate %</th>
<th>2-years control %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumours</td>
<td>128</td>
<td>48</td>
<td>37 ± 5</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rad alone</td>
<td>65</td>
<td>35†</td>
<td>28 ± 6†</td>
</tr>
<tr>
<td>Rad + Heat</td>
<td>63</td>
<td>62†</td>
<td>46 ± 8†</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Gy</td>
<td>60</td>
<td>40†</td>
<td>25 ± 6†</td>
</tr>
<tr>
<td>27 Gy</td>
<td>68</td>
<td>56†</td>
<td>56 ± 6†</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4 cm</td>
<td>81</td>
<td>54</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>&gt; 4 cm</td>
<td>47</td>
<td>38</td>
<td>29 ± 9</td>
</tr>
</tbody>
</table>

†p < 0.05

Table 4. Final multivariate analysis of tumour response.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stepwise logistic regression analysis using complete response as endpoint</th>
<th>Cox proportional hazard analysis using 2-year local control as endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-Value</td>
<td>Relative risk</td>
</tr>
<tr>
<td>Hyperthermia (rad + heat versus rad alone)</td>
<td>0.0015</td>
<td>4.01 (1.77–9.08)†</td>
</tr>
<tr>
<td>Tumour size (largest diameter in cm)</td>
<td>0.0048</td>
<td>0.77 (0.65–0.91)</td>
</tr>
<tr>
<td>Radiation dose (27 versus 24 Gy)</td>
<td>0.049</td>
<td>2.31 (1.03–5.16)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.018</td>
<td>2.81 (1.23–6.41)</td>
</tr>
<tr>
<td>Time to recurrence (months)</td>
<td>0.41</td>
<td>not estimated</td>
</tr>
<tr>
<td>Tumour localization (Node versus cutaneous)</td>
<td>0.56</td>
<td>not estimated</td>
</tr>
<tr>
<td>No. of tumours (Multiple versus single)</td>
<td>0.65</td>
<td>not estimated</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.65</td>
<td>not estimated</td>
</tr>
</tbody>
</table>

†95% confidence limits.

which in most patients was persistent. Only 16 tumours regrew after a median response time of 10 months. This figure was independent of whether the patient obtained partial or complete response and was not influenced by the addition of hyperthermia. The combined heat and radiation treatment had, however, a significantly higher complete response rate than tumours treated with radiation alone (Table 3). The response rate was also significantly better in patients given 27 Gy compared to 24 Gy. Although small tumours had a 54% complete response rate versus 38% in tumours >4 cm, this difference was not statistically significant in a univariate analysis. A multivariate logistic regression analysis using complete response as endpoint (Table 4) did show that hyperthermia resulted in a highly significant benefit of treatment and also tumour size when evaluated as largest diameter, radiation dose, and sex were of significant influence. This is also seen when analysing the outcome in the two stratification parameters (Figure 1) where a dose-response relationship was found for the two treatment arms. A logit analysis performed on the complete response data yields a similar enhancement ratio of 1.12 (95% confidence limits; 1.02–1.24). Also the tumour volume was of importance and
when comparing the effect of hyperthermia in small or large tumours it was apparent that especially tumours <4 cm which received combined treatment had a very impressive response (Figure 1). In large tumours this difference was not found to the same extent.

Although the survival time in many of these patients is limited, the persistent local control was also evaluated using the actuarial 2-year control rate as endpoint. As seen in Figure 2, the difference in tumour control between radiation alone and radiation + heat is persisting in accordance with the low number of failures. A similar univariate analysis (Table 3) shows also a significant difference as a function of dose, whereas size evaluated as above or below 4 cm was not significantly different. A Cox multivariate analysis (Table 4) revealed that additional hyperthermia, small tumour size, and high dose all were good independent prognostic parameters. In this analysis sex was not significant (p = 0.15). Neither did any of the multivariate analyses show significant influence of whether the patients had a single or multiple tumours, of the
Figure 3. Response in comparable paired tumours from same patient. The tumours were selected to belong to same size strata (above or below 4 cm) and was given same radiotherapy (24 or 27 Gy), but with or without hyperthermia. The correlation is highly significant ($P = 0.014$; McNemar's test).

Table 5. Acute and late radiation reaction in skin.

<table>
<thead>
<tr>
<th></th>
<th>Rad alone</th>
<th>Rad + heat</th>
<th>All tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (93 fields)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/slight</td>
<td>51</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td>moderate/severe</td>
<td>49</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>Late (57 fields)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none/slight</td>
<td>72</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>moderate/severe</td>
<td>28</td>
<td>37</td>
<td>33</td>
</tr>
</tbody>
</table>

time from primary tumour to the recurrence of the treated lesion, or whether it was a lymph node or cutaneous lesion.

Since there may be an individual variation in the radiation sensitivity for malignant melanoma (Bentzen et al. 1989), an analysis was performed on patients with multiple comparable lesions. Figure 3 shows the response in paired lesions from the same patients. The paired tumours were selected to be of same strata (below or above 4 cm) and were given same radiation dose (24 Gy or 27 Gy) but with or without hyperthermia. As seen in Figure 3, all the heated lesions with one exception responded better or equally to the lesions given radiation alone, resulting in a highly significant benefit of hyperthermia ($p = 0.014$; McNemar's test).

3.3. Compliance and complications

The compliance to radiation was good, and all patients received the planned treatment. The acute radiation toxicity was acceptable and not significantly different in the two treatment arms, neither did radiation induced late fibrosis differ in the two treatment arms (Table 5).

The hyperthermic treatment was more troublesome. The heating technique was a single applicator using electromagnetic heating with frequencies ranging from 144 to 915 MHz. Thermometry was performed as described in the ESHO quality assurance
guidelines with thermocouples, thermistors or Luxtron probes. The number of temperature points in tumours range from 0 to 19 (median 4), and the number of points in surrounding normal tissue range from 0 to 100 (median 2). The lack of temperature measurements in some tumours and normal tissues were due to failure in the recording system. Only active probes have been recorded.

All but four of the tumours randomized to hyperthermia received all three treatments (one tumour was not heated at all, three received only two heat sessions). The hyperthermia was in general well-accepted and in 73% of the treatments, no pain nor discomfort were noted. Slight pain was observed in 13% of the heat sessions, moderate pain in 8%, and only in 6% of the treatments the pain was so severe that the treatment was interrupted or stopped.

3.4. Thermal parameters and quality of hyperthermia

One hundred and forty-two of the 170 treatments, in which some or all quality assurance data are available, completed the planned overall treatment time (84%). The reporting in this multicentre trial did not allow a detailed analysis of individual temperature data in the tumours. The only information available was for each heat treatment, the minimal ($T_{\text{min}}$) and the maximal ($T_{\text{max}}$) heating time estimated in equivalent minutes at 43°C. In the normal tissue the maximal temperature was recorded ($T_{\text{norm}}$) and the number of temperature measurement points in both tumour and normal tissues were recorded. Tumour temperature data were achievable for 168 individual treatments, and normal tissue data were recorded in 90 treatments. The remaining data were not available either due to technical failure or loss of information in the computer.

Figure 4 shows an overview of the achieved temperatures and their mutual relationship. In 62% the maximal tumour temperature ($T_{\text{max}}$) reached the planned level (> 60 min Eq. 43°C) with a median of 68 min, range 0–1000). However, only in 9% the minimal measured tumour temperature was above that level, and in general the value was very low with a median of 9 min Eq. 43°C (range 0–219). Thus, by far most of the tumours did not obtain the planned treatment. The normal tissue was in general kept at the low temperature level, and only 17% of the treatments resulted in an equivalent temperature of above 43°C (median 7, range 0–312).

As indicated in Figure 4, the quality of the heating was far below the aim put forward in the protocol. Thus, in only 9% of the heat treatments the therapeutic aim
Table 6. Spearman rank correlation and statistical analysis of 168 heat treatments.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T_{\text{max}}$</th>
<th>$T_{\text{norm}}$</th>
<th>no. probes</th>
<th>Treatment number</th>
<th>Tumour size (diameter)</th>
<th>Tumour depth under skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{min}}$</td>
<td>$\rho = 0.450$</td>
<td>$\rho = 0.178$</td>
<td>$\rho = -0.382$</td>
<td>$\rho = 0.033$</td>
<td>$\rho = -0.176$</td>
<td>$\rho = -0.217$</td>
</tr>
<tr>
<td>P &lt; 0.0001</td>
<td>P = 0.092</td>
<td>P &lt; 0.0001</td>
<td>P = 0.662</td>
<td>P = 0.022</td>
<td>P = 0.005</td>
<td></td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>$\rho = 0.1918$</td>
<td>$\rho = 0.054$</td>
<td>$\rho = -0.053$</td>
<td>$\rho = 0.041$</td>
<td>$\rho = 0.014$</td>
<td></td>
</tr>
<tr>
<td>P = 0.070</td>
<td>P = 0.488</td>
<td>P = 0.489</td>
<td>P = 0.563</td>
<td>P = 0.854</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QUALITY ASSURANCE IN MALIGNANT MELANOMA

Best heating in 168 individual heat treatments

![Figure 5](image)

Figure 5. Relationship between the $T_{\text{max}}$ and $T_{\text{min}}$ in 168 heat treatments. The correlation is highly significant ($P < 0.0001$, Spearman). The dashed lines separate between treatments above or below 60 min Eq. 43°C, and indicate the number of sufficient and insufficient heat treatments.

was achieved. In order to analyse the parameters responsible for this insufficiency a number of factors were analysed. Table 6 shows the relationship between $T_{\text{max}}$, $T_{\text{min}}$, $T_{\text{norm}}$, tumour size (greatest diameter), and tumour depth under surface. In addition, the relationship between the temperature parameters and number of heat fractions were analysed. As seen, there is a strong correlation between the maximal and minimal temperature, which is also apparent from Figure 5 where the detailed temperature information is shown. There is, however, no correlation between neither minimal nor maximal tumour temperature and the normal tissue temperature, probably because active skin cooling has been applied in a number of cases. The tumour size and its depth are of importance and high minimal temperature seems more likely to be achieved in small tumours, and especially in tumours close to the surface. This relationship was not observed between tumour size and maximal temperature. A significant relationship between number of temperature measurement points and $T_{\text{min}}$, but not $T_{\text{max}}$, was observed.

In order to evaluate the quality of the heating and which temperature parameters may be most relevant for determining the outcome of treatment, an analysis has been performed in the tumours in which sufficient temperature data were available. This included 54 evaluable heated tumours which were analysed together with the 65
Table 7. Prognostic importance of various temperature parameters describing the heating quality. Univariate and final multivariate levels of significance are given for data analysed by stepwise logistic regression analysis using CR as endpoint and by Cox proportional hazard analysis using 2-years local control probability.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Logistic regression</th>
<th>Cox proportional hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate P-Value</td>
<td>Multivariate P-Value</td>
</tr>
<tr>
<td>T_{max}/any, continuous</td>
<td>0.027</td>
<td>0.29</td>
</tr>
<tr>
<td>T_{max}, median</td>
<td>0.018</td>
<td>0.84</td>
</tr>
<tr>
<td>Av-T_{max}, continuous</td>
<td>0.08</td>
<td>0.21</td>
</tr>
<tr>
<td>Av-T_{max}, median</td>
<td>0.018</td>
<td>0.009</td>
</tr>
<tr>
<td>T_{min}/any, continuous</td>
<td>0.27</td>
<td>0.65</td>
</tr>
<tr>
<td>T_{min}, median</td>
<td>0.019</td>
<td>0.94</td>
</tr>
<tr>
<td>Av-T_{min}, continuous</td>
<td>0.25</td>
<td>0.64</td>
</tr>
<tr>
<td>Av-T_{min}, median</td>
<td>0.012</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Figure 6. Effect of heating quality. Tumour control probability after treatment with radiation alone or combined with high or low dose hyperthermia above or below the median value of Av-T_{max}. Data from 65 non-heated and 54 heated tumours where sufficient temperature data were available.
Average value of best heat treatments in 54 tumors

Figure 7. The values and relationship between $T_{\text{max/any}}$ and $T_{\text{min/any}}$ (top) and between $\text{Av-}T_{\text{max}}$ and $\text{Av-}T_{\text{min}}$ (bottom) for 54 heated tumours with evaluable data. The dashed lines separate between treatments above or below 60 min Eq. 43°C, and indicate the number of sufficient and insufficient heat treatments.

according to whether they are above or below the median $\text{Av-}T_{\text{max}}$ value. A significant dose-response relationship for the heat effect was observed, and tumours achieving the best hyperthermia showed a superior local control probability.

The values and relationship between the $T_{\text{max/any}}$ and $T_{\text{min/any}}$, as well as between the $\text{Av-}T_{\text{max}}$ and $\text{Av-}T_{\text{min}}$ are shown in Figure 7. Only in six respective three of the 54 heated tumours did the $T_{\text{min/any}}$ and $\text{Av-}T_{\text{min}}$, respectively, reach the required values. Similarly was sufficient values of $T_{\text{max/any}}$ and $\text{Av-}T_{\text{max}}$ not obtained in nine and 15 tumours respectively. In fact, only two of the analysed tumours received a $T_{\text{min}}$ of > 60 min Eq. 43°C in all three heat treatments, and only in 22 tumours was that true for values of $T_{\text{max}}$. 

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3.5. Survival

The overall 5-year survival rate of the patients was 19% (Figure 8). Local treatment of patients with advanced and eventually multiple metastatic lesions from malignant melanoma may seem redundant without major benefit for the patients. However, univariate analysis of patient survival indicated that if all known disease in the patients were treated, and if the outcome was persistent local control, the patient had a highly significant better survival probability than patients with known disseminated disease and/or lack of local control. Figure 8 shows that 38% of the patients have a 5-year survival probability if all known disease was controlled (independent of the treatment given), compared to 8% in the patients with persistent active disease (the last patient in this group died after 63 months) \((p = 0.002)\). Also sex was of prognostic importance with a 5-year survival of 30% in women compared to 8% in men \((p = 0.008)\). Similarly, patients with single tumours survived significantly longer than patients with multiple lesions (5-year survival of 24 versus 13%; \(p = 0.007\)), whereas the time to recurrence of lesions did not significantly
Table 8. Cox proportional hazard analysis of 68 patients using death as endpoint.

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-Value</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control of all lesions</td>
<td>0.006</td>
<td>0.42 (0.22–0.81)†</td>
</tr>
<tr>
<td>(yes versus no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.019</td>
<td>0.51 (0.30–0.89)</td>
</tr>
<tr>
<td>No. of tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Multiple versus single)</td>
<td>0.035</td>
<td>1.94 (1.10–3.42)</td>
</tr>
<tr>
<td>Tumour localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Node versus cutaneous)</td>
<td>0.17</td>
<td>not estimated</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>0.51</td>
<td>not estimated</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.66</td>
<td>not estimated</td>
</tr>
</tbody>
</table>

†95% confidence limits.

influence the survival probability. These univariate observations were confirmed in a Cox multivariate analysis (Table 8).

4. Discussion
The ESHO 3-85 protocol, which is the first completed randomized study comparing the effect of adjuvant hyperthermia to radiotherapy in a single histopathological tumour type, confirmed that hyperthermia significantly enhances the effect of radiation, both evaluated as complete response and persistent local control. The benefit of the combined treatment was in the same order as that previously described in uncontrolled studies (Overgaard 1981, Kim et al. 1982, Gonzalez Gonzalez et al. 1986, Arcangeli et al. 1987, Overgaard and Overgaard 1987, Emami et al. 1988, Engin et al. 1992). The trial also confirms that total dose of radiation and tumour volume were other prominent prognostic factors (Bentzen et al. 1989, Overgaard and Bentzen 1990). In addition, we observed that female sex was beneficial for complete response, whereas the number of tumours in each patient, the type of lesions and the time between primary tumour and the development of the recurrence treated here appeared to be unimportant.

As seen in other clinical trials with hyperthermia, the heating technique is the Achilles heel also in the present study. All patients achieved the planned radiotherapeutic treatment but a sufficient dose description of hyperthermia was impossible to obtain. Thus, only 9% of the heat treatments were in accordance with the protocol requirement. Nevertheless, the quality of the heating is of the same magnitude as that described in previous studies where these parameters have been recorded (Perez et al. 1989, Ben-Yosef and Kapp 1993). The philosophy behind the European Society for Hyperthermic Oncology’s clinical trials (Overgaard 1987, Arcangeli et al. 1988) has been to challenge the heating techniques which in previous non-controlled studies have indicated a potential benefit (Overgaard 1989, Overgaard and Bach Andersen 1995) in a phase III randomized study. Certainly, such policy has its shortcomings, but rather than continuing to optimize the heating ability while constantly being subjected to uncontrolled claims of efficiency, we have felt a need for conducting a randomized trial which would evaluate the clinical ability of the current heating equipment. This does imply that the efforts towards obtaining better heating of tumours should be ceased, but such development can only take place if it is supported by biological and clinical data which can provide a useful rationale and indication for a better quality of hyperthermic therapy.
Since the various thermal parameters are related (Table 6) it is obvious that when one parameter (Av-\(T_{\text{max}}\)) was allowed to dominate in a multivariate analysis, it must take place at the expense of the others. In fact, if Av-\(T_{\text{min}}\) was forced into the model, this also became significant and the Av-\(T_{\text{max}}\) would lose its power. This relationship is supported by the strong correlation described in Figure 5. It is interesting to note that the Av-\(T_{\text{max}}\) is a stronger prognostic parameter for outcome than information of whether or not the tumour has been heated, and therefore points towards the importance of heating quality as the dominating factor. Figure 6 shows this tendency.

In this figure the heated tumours have been divided according to whether they are above or below the median Av-\(T_{\text{max}}\) value. It is seen that there appears to be a dose-response relationship for the heat effect, and that tumours achieving the best hyperthermia appears to have the best tumour control probability. This agrees with the result from a uncontrolled study in malignant melanoma (Ben-Yosef and Kapp 1993), and which is also supported by the data with hyperthermic brain implants where a hyperthermic dose-response relationship was observed (Sneed et al. 1994).

Many thermal parameters and characteristics have in non-controlled studies been observed to be of prognostic value (Valdagni et al. 1988, Cox and Kapp 1992, Overgaard and Bach Andersen 1995), and the dominating thermal parameter may very well be strongly influenced by the temperature measurement techniques. However, all studies stress the importance of adequate heating, as also demonstrated in the current trial.

The volume effect was interesting to the extent that smaller tumours did respond better than larger, but the effect of hyperthermia was especially seen in tumours < 4 cm in diameter. This finding is in accordance with the findings in the RTOG 81-4 study, where it was observed that especially the small tumours (< 3 cm) had the benefit of combining hyperthermia with radiation, probably due to a better ability to heat these lesions (Perez et al. 1989, 1991). The same situation may exist in the ESHO 3-85 protocol, since the heating quality (\(T_{\text{min}}\)) was significantly poorer in large tumours (Table 6).

Of interest is the significant relationship between number of temperature measurement points and minimal tumour temperature. This parameter is decreasing with increasing number of temperature points, whereas the maximal temperature is independent of this parameter. This relationship is of course understandable since an increasing number of temperature measurements are likely to detect a cold spot, whereas the maximal temperature normally occurs in the centre of the tumour where there normally always is placed a temperature probe. These data clearly demonstrate that in order to obtain comparable temperature quality data the thermometry must be standardized. There was no correlation between the number of heat fractions and the outcome of treatment, and an anticipated hypothesis that the first treatment tends to break down the blood circulation, allowing a better heating in the subsequent sessions, could not be confirmed in this study.

The complications to treatment were minor and acceptable and despite most heat treatments being given within half an hour after radiation, this did not result in any substantial enhanced radiation damage, probably due to the use of active skin cooling in most cases.

Despite a collective effort by numerous European institutions, it took about 6 years to recruit the required number in the present trial and almost half of the patients were included from two institutions. This is an illustration of the problems with hyperthermic oncology (Arcangeli et al. 1988, Overgaard 1990, Curran and...
Goodman 1992, Dewhirst et al. 1993, Dewey 1994), namely that rather than to perform a joint effort in making a proper evaluation of this biologically promising modality, many institutions conduct their activities independently, which in general has led to non-conclusive results. It is our hope that the current results in addition to its clinical results also will be recognized for demonstrating the usefulness of international collaboration.

Most of the initial European collaborative trials have now be completed. In addition to the ESHO 3-85 study on malignant melanoma hyperthermia has also been found to significantly enhance the effect of radiotherapy in the treatment of recurrent breast carcinoma in the chestwall, and in advanced pelvic tumours (Overgaard et al. 1995b, International Collaborative Hyperthermia Group 1995).

5. Conclusion

Overall the treatment yielded a high response rate and resulted in a significant palliative effect in most patients, irrespective of the treatment schedules. Univariate and multivariate analysis both showed that adjuvant hyperthermia significantly improved local tumour control when applied in association with few large radiation fractions in the treatment of malignant melanoma. Also tumour size and dose of radiation were found to be of significant prognostic importance. The effect of adjuvant hyperthermia was related to the extent of heating achieved. Hyperthermia did not enhance the early or late radiation morbidity (due to active skin cooling). Compliance and tolerance to hyperthermia was good, but the quality of the heating was poor, and most tumours did not receive the prescribed heat dose.

Univariate and multivariate analysis both showed that good survival probability was associated with female sex, number of malignant lesions and most importantly, persistent control of all known disease at time of treatment. In other words, successful local treatment to patients with a single or a few metastatic malignant melanoma lesions may be curative in approximately half of these patients.

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