Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma

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Summary

The value of hyperthermia as an adjuvant to radiotherapy in patients with malignant melanoma was studied in a European multicentre trial.

134 metastatic or recurrent lesions of malignant melanoma in 70 patients were randomly assigned to receive radiotherapy (three fractions of 8 Gy or 9 Gy in 8 days) alone or followed by hyperthermia (43°C for 60 min). Overall, the 2-year actuarial local tumour control was 37(SE 5)%. Univariate analysis showed a beneficial effect of hyperthermia (radiation alone 28% *vs* combined treatment 46%, p=0·008) and radiation dose (24 Gy 25% *vs* 27 Gy 56%, p=0·02), but no effect of tumour size (≤4 cm 42% *vs* >4 cm 29%, p=0·21). Cox multivariate regression analysis showed the most important prognostic variables to be hyperthermia (odds ratio for 2-year local control 1·73 [95% CI 1·07–2·78], p=0·023), tumour size (0·91 [0·85–0·99], p=0·05), and radiation dose (1·17 [1·01–1·36], p=0·05). Addition of heat did not significantly increase acute or late radiation reactions. Heating was well tolerated, but because of difficulties with equipment only 14% of treatments achieved the protocol objective. The overall 5-year survival rate was 19%, but 38% of the patients for whom all known disease was controlled survived 5 years.

Adjuvant hyperthermia significantly improved local tumour control when applied in association with radiation in treatment of malignant melanoma. Successful local treatment of patients with a single or a few metastatic malignant melanoma lesions has significant curative potential.

Lancet 1995; **345:** 540–43

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Introduction

The biological rationale for combining hyperthermia with radiation is based on two different mechanisms—hyperthermic radio-sensitisation and direct hyperthermic cytotoxicity against radio-resistant cells.[1,2] So that both mechanisms can be utilised the interval between radiation and hyperthermia must be as short as possible, but a short interval carries the risk of increasing normal tissue damage also, since hyperthermic radio-sensitisation is found in both tumour and normal tissues. A differential heating pattern is therefore required, for example by active skin cooling.

Despite difficulties in providing homogeneous heating to a given tumour area, there have been many uncontrolled studies in which combined heat and radiation were applied. Most have suggested a significant advantage of the combination over radiation alone.[1,3] The benefit could be obtained without increasing normal tissue morbidity if the interval between the two modalities was not too short or if the tumours were heated (semi)selectively.

Recurrent or metastatic malignant melanoma responds well to radiotherapy given in large doses per fraction,[4,5] and uncontrolled studies suggest that adjuvant hyperthermia can improve this response.[6–9] This tumour type may therefore be a suitable clinical model for investigations of the interaction between radiotherapy and hyperthermia. In January, 1986, the European Society for Hyperthermic Oncology (ESHO) initiated a multicentre randomised clinical trial with the aim of assessing the efficacy of local hyperthermia given as adjuvant to radiotherapy in the treatment of advanced malignant melanoma lesions, the probability of tumour response and local control, early and late tolerance in normal tissues, and the feasibility of various heating techniques.[10]

Patients and methods

Eligible patients had advanced, recurrent, or metastatic lesions of non-lentiginous malignant melanoma; were expected to be candidates for radiotherapy; had life-expectancy longer than 3 months; and were not receiving other concurrent cancer therapy (especially chemotherapy). We required that the treated areas had not previously been treated with radiation and that all lesions included could be heated with the available equipment. The study was carried out according to the Helsinki Declaration II. In addition, the protocol was adapted and approved by all relevant national and local ethics committees.

Since many patients with this disorder have multiple lesions and the treatment applied was local, the protocol was designed to allow inclusion of multiple lesions in the same patient. Tumours were stratified by centre and according to size (≤4 *vs* >4 cm in largest diameter) and randomly assigned either radiotherapy alone (three fractions of 8 or 9 Gy with 4 days' interval [Monday/Friday/Tuesday]) or the same radiotherapy with each fraction followed within 30 min by hyperthermia (minimum tumour treatment temperature 43·0°C in 30 min).

	Radiation (n=65)	Radiation plus hyperthermia (n=63)
Tumour size		
Median (range) in cm	3 (1–14)	3 (1–13)
Number ≤4 cm	41	40
Number >4 cm	24	23
Median (range) depth under skin in cm	2 (1–7)	2 (1–7)
Number receiving		
24 Gy	31	29
27 Gy	34	34
Number of patients with single tumour	15	22
Median (range) number of tumours per patient	2 (1–7)	2 (1–7)
Site		
Lymph node	19	19
Skin/subcutis	49	44
Type		
Local recurrence	9	7
Metastasis	56	56
Median (range) time in months		
To recurrence	14 (0–113)	13 (0–203)
Observation time	7 (3–65)	9 (3–73)
Number of tumours in female patients	26	26
Median (range) age of patients in years	57 (32–88)	59 (19–88)

Table 1: **Characteristics of 128 evaluable tumours**

Randomisation was arranged centrally. In patients with multiple tumours, each tumour was given a consecutive number before randomisation. All odd-numbered tumours were randomised independently, and even-numbered lesions were matched with the preceding lesion to form a pair receiving the same radiation dose but with opposite assignments to radiation alone and radiation with heat.

Radiation was applied with electrons or high-voltage photons through one or multiple portals. Radiation therapy doses were prescribed as specified in ICRU-29.[11] Hyperthermia was applied with microwave or radiofrequency equipment. There were no limitations on the equipment used except that it had to be able to provide a tumour temperature of 43·0°C. Active skin cooling was allowed. The heat treatment was applied after each of the radiation fractions, starting within 30 min. We specified that efforts should be made to avoid heating of normal tissue or to apply appropriate skin cooling. Hyperthermia and multi-point thermometry in both tumour and normal tissue were carried out in accordance with the ESHO quality assurance guidelines.[12] The time and temperature were recorded and a heat dose in equivalent minutes at 43°C was calculated.[5,12]

The endpoints of the study were complete response[13] (at 3 months) and persistent local control as well as acute and late normal tissue damage.[14] All time estimates used the date of randomisation as the baseline.

The statistical analysis was based on the described dose-response relation for both radiation alone and combined radiation and hyperthermia,[1] which suggested that after addition of hyperthermia a 30% improvement in local control could 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 more than 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.

In patients with multiple lesions, an independent evaluation of tumour control was done within each radiation field and at each follow-up. Whenever possible follow-up of the other treated lesions was continued after the time of the first local failure. There is a tendency for treated lesions within an individual to have similar outcomes.[15] We decided, therefore, that the most conservative approach would be randomly to assign the different treatments to pairs of tumours in an individual. The standard assumption of statistical independence between the tumours is therefore not strictly valid. It is not straightforward to correct for the association in the data analysis; however, because more than half of the patients had only 1 tumour and because each lesion was followed independently, this matching of multiple lesions is unlikely to have had an important influence on the estimated treatment effects.

	Number of tumours	Complete response rate (%)	2-year control (SE) (%)
All tumours	128	48	37 (5)
Treatment			
Radiation	65	35*	28 (6)*
Radiation plus hyperthermia	63	62*	46 (8)*
Dose			
24 Gy	60	40*	25 (6)*
27 Gy	68	56*	56 (6)*
Size			
≤4 cm	81	54	42 (6)
>4 cm	47	38	29 (9)

*$p<0·05$.

Table 2: **Univariate analysis of initial complete response and 2-year actuarial local control**

The primary endpoint was persistent local control, estimated by Kaplan-Meier analysis with the Mantel-Cox test for comparison. Frequencies were compared by χ^2 test. Multivariate analyses of local control were by the Cox proportional hazards model and those of complete response at 3 months were by logistic regression analysis. The treatment effect was examined by the intention-to-treat principle, and evaluable lesions were included in the randomisation group whether or not the planned treatment had been completed. In addition to the analysis of the randomised tumours the influence on patient survival of local tumour response and other prognostic variables was investigated.

Results

134 lesions in 70 patients were randomised between January, 1986, and May, 1992. 128 lesions (68 patients) were evaluable for analysis. 1 patient had 2 lesions removed by surgery before first follow-up (1 each treatment). 1 patient refused to take part after randomisation (1 lesion randomised to radiation), and 3 lesions were never evaluated because the patient died before first follow-up (2 combined treatment, 1 radiation). 33 of the 68 patients were female. 37 patients had a single tumour, and 32 had multiple (2–7) treated lesions. The observation time ranged from 3 to 73 months. Tumour characteristics are given in table 1.

Overall, treatment yielded a high response rate and resulted in a significant palliative effect in most patients, irrespective of treatment group. 103 (80%) tumours showed complete or partial responses, which in most patients were persistent. Only 16 tumours regrew after a median response time of 10 months. This time was independent of whether the patient had had partial or complete response and was not influenced by the addition

	p	Relative risk (95% CI)
Hyperthermia (combined treatment *vs* radiation alone)	0·0015	4·01 (1·77–9·08)
Tumour size (largest diameter in cm)	0·0048	0·77 (0·65–0·91)
Radiation dose (27 *vs* 24 Gy)	0·049	2·31 (1·03–5·16)
Sex (female)	0·018	2·81 (1·23–6·41)
Time to recurrence (months)	0·41	· ·
Tumour site (node *vs* cutaneous)	0·56	· ·
Number of tumours (multiple *vs* single)	0·65	· ·
Age (years)	0·65	· ·

Table 3: **Stepwise logistic regression analysis with complete response as endpoint**

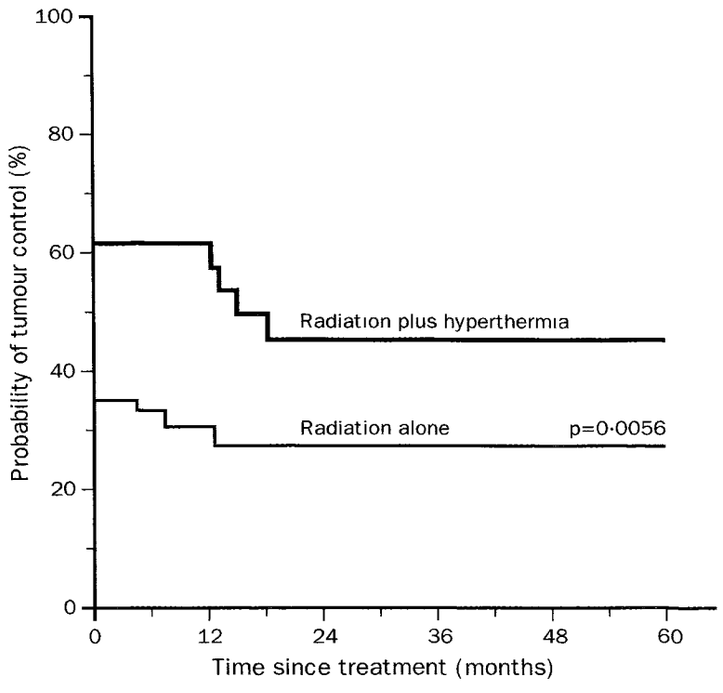

Figure: **Probability of tumour control after treatment with radiation alone or radiation plus hyperthermia**

of hyperthermia. The combined heat and radiation treatment had, however, a significantly higher complete response rate than treatment with radiation alone (table 2). Similarly, the response rate was higher in patients given 27 Gy than in those given the lower dose and in small tumours than in larger tumours. Multivariate logistic regression analysis with complete response as endpoint (table 3) showed a highly significant benefit of hyperthermia treatment; tumour size, radiation dose, and sex also had significant effects. Although the survival time in many of these patients is limited, persistent local control was evaluated with the actuarial 2-year control rate as endpoint. The difference in tumour control between radiation alone and combined with hyperthermia is persisting in accordance with the low number of failures (figure). A similar univariate analysis (table 2) showed a significant difference as a function of dose, whereas tumour size had no significant effect. A Cox multivariate analysis (table 4) showed that additional hyperthermia, small tumour size, and high dose were all independent prognostic variables. In this analysis sex was not significant. No multivariate analysis showed a significant effect of single or multiple tumours, time from primary tumour to recurrence of the treated lesion, or site of tumour.

Compliance with radiotherapy was good, and all patients received the planned treatment. Both acute and late adverse effects were acceptable and did not differ significantly between the two treatment groups. All but 4 of the tumours randomised to hyperthermia received all three treatments (1 tumour was not heated at all, 3 received only two heat sessions). The hyperthermia was in general well accepted; in 73% of the treatments, no pain or discomfort were noted and only 6% caused pain severe enough to interrupt or stop treatment. 84% of the heat sessions lasted the required time. In 61%, the maximum tumour temperature reached the planned value, but in only 14% of treatments was the minimum measured tumour temperature above the threshold value. Thus, most of the tumours did not receive the planned treatment. The normal tissue was in general kept at low temperatures, and only 18% of treatments resulted in an equivalent temperature of more than 43°C.

	p	Relative risk (95% CI)
Hyperthermia	0·023	1·73 (1·07–2·78)
Tumour size (largest diameter in cm)	0·050	0·91 (0·85–0·99)
Radiation dose (27 *vs* 24 Gy)	0·049	1·17 (1·01–1·36)
Sex (female)	0·15	..
Time to recurrence (months)	0·24	..
Tumour site (node *vs* cutaneous)	0·79	..
Number of tumours (multiple *vs* single)	0·63	..

Table 4: **Cox proportional hazard analysis with 2-year local control as endpoint**

The overall 5-year survival rate of the patients was 19%. Survival was, however, greater for 23 patients in whom all known disease was controlled than for the 47 patients with persistent active disease (38 *vs* 10%). 5-year survival was 31% in women compared with 8% in men (p=0·005). Similarly, patients with single tumours survived significantly longer than those with multiple lesions (24 *vs* 15%, p=0·017), whereas the time to recurrence of lesions did not significantly influence the survival probability. These univariate observations were confirmed in a Cox multivariate analysis in which the significant prognostic variables for survival were local control of all known disease (odds ratio 2·28 [95% CI 1·18–2·78], p=0·009), being female (1·26 [1·05–1·51], p=0·013), and a single lesion (2·04 [1·15–3·57], p=0·024).

Discussion

This randomised investigation of the effect of adjuvant hyperthermia in a single histopathological tumour type confirmed that hyperthermia significantly enhances the effect of radiation, evaluated as either complete response or persistent local control. The benefit of the combined treatment was of the order of that reported in uncontrolled studies.[6–8] The trial also confirms that total dose of radiation and tumour volume are important prognostic factors.[9,15]

Smaller tumours responded better than larger tumours, but the effect of hyperthermia was especially pronounced in tumours less than 4 cm in diameter. This finding accords with the results of Perez and colleagues' study,[16,17] that smaller tumours responded better to adjuvant hyperthermia because it is easier to heat such lesions. Although the quality control in our trial has not been completed, our impression is that the same is true of our trial, and too much has been expected of the heating ability of the equipment.[16,18,19]

As in other clinical trials with hyperthermia, the heating technique was the weak point. The planned radiotherapy was achieved in all patients but a sufficient dose description of hyperthermia was impossible to obtain. Thus, only 14% of the heat treatments were in accordance with the protocol requirement. Nevertheless, the quality of the heating is similar to that described in uncontrolled studies.

The trial showed that radiotherapy given in a few large fractions can control a large proportion of malignant melanoma lesions. The treatment is convenient because few fractions are needed. A treatment with 24–27 Gy in three fractions may seem trivial but is equivalent to about 70 Gy in conventional fractionation in terms of late tissue reactions.[4] Thus care should be taken with such a schedule, especially if sensitive organs or tissues are within the treatment field.[9]

Complications were acceptable and, with the exception of a few heat-induced burns or ulcerations, there was no significant difference in early damage between areas treated with radiation or with radiation combined with hyperthermia, in agreement with the experience of others.[20] Although most heat treatments were given within 30 min of radiation, there was no enhancement of radiation damage, probably because active skin cooling was used in most cases.

The finding that patients who achieve persistent local control in all known disease at the time of treatment will have a good survival probability accords with previous observations after similar lesions have been treated with either radiation or surgical excision.[4,5,9,21,22] Thus, between a third and half of such patients can be expected to be alive after 5 years, which suggests that patients with recurrent malignant melanoma should be considered candidates for curative therapy. Our study also confirms that women had a significantly better prognosis than men and patients with a single lesion did better than those with multiple lesions.[21,23,24] We did not confirm that a long time between diagnosis and recurrence[21] was beneficial.

The following departments also took part in the study: Oncologica Medica, Ospedale S Maria della Croci, Ravenna, Italy (G Cruciani); Istituto Regina Elena, Rome, Italy (F Di Filippo); Department of Radiotherapy, Institute of Oncology, Warsaw, Poland (J Fijuth); Institut Curie, Paris, France (C Jaullery); MRC Cyclotron Unit, Hammersmith Hospital, London, UK (C C Vernon); Christie Hospital, Manchester, UK (R D James); and Department of Radiotherapy, University of Freiburg, Germany (R Engelhardt).

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