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● *Phase I/II Studies*

RETROSPECTIVE ANALYSIS OF HYPERTHERMIA FOR USE IN THE PALLIATIVE TREATMENT OF CANCER: A MULTI-MODALITY EVALUATION

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Forty-two patients with local or superficial metastatic or recurrent malignant tumors were treated in a non-randomized Phase I/II study to assess the tumoricidal effects of heat combined with radiation and/or chemotherapy. Radiation doses administered averaged 3130 ± 350 cGy; chemotherapeutic agents employed included bleomycin, mitomycin-C, adriamycin, and cis-platin, heat was induced by radiative or interstitial microwave applicators operating at frequencies ranging from 95 to 900 MHz. Forty-one of the forty-two patients were evaluated for initial therapeutic effects yielding the following response distributions: local hyperthermia with radiation—42% complete response (CR), 44% partial response (PR), and 15% no response (NR); local hyperthermia with chemotherapy—0% CR, 50% PR and 50% NR. Long-term response duration was evaluated for local hyperthermia with radiation, yielding mean time to recurrence of 9.4 months for CR's and mean time to progression of 3.4 months for PR's. In retrospective analysis, we examined the correlations of previously established response-predictor variables of tumor volume and minimum thermal dose with both initial and long-term response rates. Initial complete response rates were correlated directly with non-site-specific minimum thermal dose, varied inversely with tumor volume and exhibited a positive correlation for a limited histologic type/treatment site combination. Surprisingly, long-term response did not correlate either with tumor volume or thermal dose. The frequency of thermally induced complications, which did not correlate with any measured thermal parameters, was found to be 42%, expressed on a per-patient basis.

Hyperthermia, Superficial, Thermal dose, Radiation, Chemotherapy.

INTRODUCTION

Hyperthermia, as a synergistic palliative adjuvant to radiation therapy, is growing in importance, as evidenced by an ever-increasing volume of published clinical data (2–4, 6, 19, 21, 22, 26, 32, 33, 36, 40). Matched lesion studies involving local or superficial tumors have shown superior tumor response to heat and radiation compared to those treated with radiation alone by as much as a factor of two (21–33, 36).

With increasing experience, it becomes clearer that identification and quantification of response predictor variables is necessary to help define the limits of the clinical usefulness of hyperthermia. Variables which have been examined as response predictors are treatment site, histology, radiation dose and fractionation scheme, tumor volume, thermal dose, method of heating and thermal gradients, the latter two predictors often being interrelated (8–10, 14, 25, 26, 37). Not surprisingly, highly positive short-term response rates do not always serve as good long-term response predictors (11). Despite the deficiencies associated with the non-rigorous application of hyperthermia in a clinical setting (non-randomization of patients, insufficient thermometry data, frequently inadequate heating, limited long-term patient follow-up, etc.) all data from clinical trials is extremely important for the advancement of hyperthermia, if for no other reason than to aid in the evaluation of heating techniques, concepts, and equipment in a non-optimal setting. The purpose of this paper, then, is to present a retrospective analysis of $3\frac{1}{2}$ years of local/superficial, non-randomized, Phase I–II hyperthermia studies at Rush-Presbyterian-St. Luke's Medical Center, evaluating clinical response in terms of previously published predictor variables (9, 10, 25, 37) and accounting for observed discrepancies where possible.

METHODS AND MATERIALS

Patient selection

Between February 1982, and October 1985, 42 patients were entered into Phase I-II hyperthermia studies, under

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specific institutional protocols, for the treatment of local/superficial neoplasms using a combination of heat plus radiation or heat plus chemotherapy. Requirements for patient eligibility included (a) histologically proven disease untreatable by standard therapy (b) presence of measurable tumor determined by radiologic and other non-invasive diagnostic techniques (c) expected survival duration of at least 3 months (d), and Karnofsky status of 50 or greater. Table 1 lists pertinent patient demographic data, including tumor histologic and volumetric distributions. Tumor volumes were calculated from three orthogonal dimensions obtained from direct physical measurement, CT and NMR scans. Typical dimensional uncertainties ranged from 10 to 30%.

Irradiation

Of the 42 patients treated, 36 underwent radiation therapy for metastastic or recurrent malignancies using 1.25 MeV photons from a ^{60}Co source, 4–18 MV photons or 6–20 MeV electrons from a linear accelerator.* Of these, 30 received radiation given in a 2-dose/week fractionation schedule, 400 cGy/fraction, normally administered prior to hyperthermia; 3 were treated under a 5-dose/week fractionation schedule, 200 cGy/fraction, prior to and interspersed between two weekly hyperthermia treatments; and 2 patients received continuous brachytherapy using ^{192}Ir. Table 2 summarizes the pertinent radiotherapy data.

Chemotherapy

Of the remaining six patients undergoing combined therapy, five did not receive radiation but were given chemotherapy with a variety of agents (see Table 2), whereas one received radiation and chemotherapy. Unlike the 2-dose/week radiation fractionation schedule, given prior to hyperthermia, chemotherapy was administered at various times relative to hyperthermia therapy: prior to, concurrently with, and after achievement of specific targeted tumor temperatures.

Table 1. Patient data

Sex	
No. of female patients	23
No. of male patients	19
Age (years)	
Mean	57 ± 14
Range	29–87
Histology	
Adenocarcinoma	16
Squamous Cell Carcinoma	12
Transitional Cell Carcinoma	1
Melanoma	4
Fibrosarcoma	3
Miscellaneous	6
Totals	42
Tumor volume (cm^3)	
Mean	194 ± 265
Range	2–1210
Disease status (% of patients)	
Metastatic	18
Recurrent	82
Primary	0

Table 2. Radiation and chemotherapy data summary

Radiation therapy	
Single fractionation schedule	(30)*
Mean dose (cGy)	3130 ± 345
Range (cGy)	2400–4000
Multiple fractionation schedule	(4)
Mean total dose (cGy)	6550 ± 412
Range (cGy)	6000–7000
^{191}Ir brachytherapy	(2)
Mean dose (cGy)	3750 ± 1060
Range (cGy)	3000–4500
Total no. of patients	36
Chemotherapy	
Bleomycin	2
Mitomycin-C	1
Adriamycin	1
Cis-Platin	1
Total no. of patients	5
Radiation therapy and chemotherapy	
Dose (cGy)	1740
Chemo agent: mitomycin-C	
Total no. of patients	1

* Numbers in parentheses are patient totals.

Hyperthermia

Local hyperthermia treatments were administered with a BSD-1000† hyperthermia system: employing a Z-80 microprocessor-controlled variable frequency generator (50–1000 MHz); a closed-loop feedback thermometry system featuring high-resistivity thermistor temperature probes; and a variety of microwave applicators.

Six types of radiative aperture applicators were employed for local hyperthermia. Nominal heating depths ranged from 0 to 3 cm at frequencies above 300 MHz. Two applicators, operating at frequencies below 200 MHz, had the capability to extend the heating depth to between 4 and 7 cm provided surface cooling was used. Heating areas varied from 2 × 2 cm^2 to a maximum of 15 × 20 cm^2, as determined by the 50% iso-power contour. Microwave coupling to patient tissue was accomplished through temperature-regulated, circulating distilled water boluses for five of the six radiative applicators. Circulating water was heated or cooled depending on the requirements for regulation of tissue surface temperatures: consistent with the protection of normal tissue from thermal damage while attempting to achieve a tumor therapeutic temperature. An interstitial applicator, inserted through a 14 ga.

* Clinac 4, Varian Radiation Division, Palo Alto, CA; Therac 20, AECL, Ottawa, Canada.

† BSD Medical Corporation, Salt Lake City, UT.

catheter, was used in tandem arrays for invasive heating of bulky or awkwardly located local tumors. Typical operating power ranged from 20 to 200 watts for the radiative aperture applicators to 4 to 15 watts per interstitial antenna.

Hyperthermia treatments were fractionated to provide a minimum of 48–72 hours between sessions to minimize the effects of induced thermal tolerance (16, 18, 23, 24). The objective in the initial heating protocol for local therapy was to elevate the tumor core temperature to 43°C ± 0.5°C for 30 minutes, or its thermal dose equivalent, while maintaining surrounding normal tissue at 42°C; this was later modified to maintain the lowest measured intra-tumor temperature at or in excess of 43°C for a minimum of 30 minutes (After the data of Dewhirst *et al.* (9) indicated the importance of the minimum tumor thermal dose as a predictor of tumor response). A complete schedule of treatments (normally 8) required 4 weeks to be completed, with individual sessions ranging in length from 45 to 90 minutes. Deviation of the normal schedule occurred in only 3 cases: a reduction to 5 for one patient; an increase to 10 sessions for two others. Individual treatments were terminated if any of the following complications occurred: (1) severe pain or any indication of thermal damage to tissue; and (2) difficulty in breathing or excess anxiety.

Thermometry and thermal dose

Temperatures were monitored continuously with calibrated high-resistivity thermistor probes. Surface temperatures were obtained from probes in direct contact with tissue, but thermally insulated from the surrounding external environment (a minimum of 2 were used for all patients); intra-tumor temperatures were monitored with probes (normally, two) inserted into percutaneous, 16-gauge, closed-end catheters[‡] which remained in place for the duration of hyperthermia treatments. Percutaneous intra-tumor temperature monitoring was excluded in 4 of the 42 patients treated because the treatment site was near the surface or close to a vital organ or major blood vessel. The treatment responses for this subgroup were included in the general response comparisons but were excluded from specific tumor thermal dose analysis comparisons.

Heating gradient profiles were obtained by manual thermal mapping at thermal equilibrium, with data points taken at 0.5 cm intervals within the closed-end catheters. After locating the position of the minimum and non-colinear maximum monitorable temperatures, probes were positioned at these points and temperature data acquired automatically for post-treatment analysis of thermal dose.

Thermal dose, expressed as 43°C equiv. min, was determined for each monitored point by means of a modified statistical algorithm.[§] Temperature data, accumulated at 10 sec. intervals, was transformed to a thermal equivalence factor, via the functional form adopted by Sapozink *et al.* (30), and integrated from the beginning to the end of treatment. No corrections or modifications to the calculated thermal dose were made for the effects of prolonged induction times, step-up or step-down heating (29, 30) and thermal mapping. The latter correction, based on the amount of time required for mapping at steady-state, was estimated to not exceed 10% of the calculated dose. Minimum and maximum thermal doses determined for each treatment were later combined to yield non-site-specific session averages.

Response end points

Patients were examined for clinical evidence of disease, beginning with the last treatment, at varying intervals approximately 2–6 weeks apart. Responses were categorized as follows: (1) CR—complete response, characterized by disappearance of clinically detectable disease; (2) PR—partial response, as evidenced by a minimum 50% tumor volume reduction; (3) NR—no response, as indicated by less than 50% tumor volume reduction; (4) NE—not evaluable, usually due to premature withdrawal from therapy. Recurrence was indicated by local reappearance of primary tumor following a CR or, disease progression following a PR with regrowth of 25% or more of the post-treatment tumor volume.

Statistical methods

Chi-square tests (5, 28) were used for examination of the dependence of initial complete and overall response rates on the variates of histology, volume and thermal dose. The dependence of response on radiation dose was not examined because of the small number of treatments that varied from a standard total dose of 3200 cGy. Simple linear regression was used to fit the data for CR vs. volume while linear logistic regression employing the method of maximum likelihood was used to obtain the best fit to the logit of the CR rate $\ln(P/(1-P))$ vs. thermal dose (7).

In addition to initial response comparisons, univariate analysis of response duration was applied to the incomplete response-survival data employing Kaplan-Meier (product-limit) survival curves (20). Statistical differences between survival curves were ascertained through logrank (27, 28) and Wilcoxon (28) statistical procedures.

RESULTS

Initial response

Of the 42 patients entered into the Phase I–II study, 41 were evaluated for initial response (within 1 month of post treatment follow-up) while the remaining patient was

[‡] Deseret Medical Corp., Salt Lake City, UT.

[§] For the BSD-1000 Z80 Microprocessor, BSD Corporation, Salt Lake City, UT.

Table 3. Initial response breakdown according to adjuvent modalities

Adjuvent therapy	Evaluable patients	Complete (%) (*)	Partial (%) (*)	None (%) (*)	Unevaluable patients
Radiation	36	15 (42)	16 (44)	5 (14)	0
Chemotherapy	4	0	2 (50)	2 (50)	1
Rad. + chemo.	1	0	0	1 (100)	0

* Percentages exclude the "unevaluable" category.

judged to be unevaluable, primarily because he did not complete the requisite course of treatments (as dictated by protocol) either due to heat intolerance or because of the toxic effects of chemotherapy on normal tissue. Table 3 lists the observed responses according to treatment modality. Although it appears that the combined modalities of heat and chemotherapy appeared to produce significantly inferior responses, when compared to heat plus radiation, the small number of patients entered into the chemotherapy arm of the study renders any such judgement as premature.

Patient response rates, stratified according to tumor histological types, are given in Table 4 for the 41 evaluated patients. Restricting the statistical analysis to responses for heat plus radiation, it becomes apparent that different tumor histologies exhibit widely varying responses to heat plus radiation (e.g. a CR of 65% for adenocarcinomas compared with an NR of 75% for miscellaneous types). This is supported by Chi-square statistical analysis which indicates that, for both overall and complete response rates, histologic characteristics, by themselves, are not a reliable predictor of response (Chi-square statistic: $0.25 < p < 0.1$). However, for squamous-cell carcinoma and adenocarcinoma, the response correlated with anatomical site (see Table 5): for tumors of the head and neck, the response for squamous-cell carcinoma was superior to other tumors (Chi-square statistic: $p < 0.01$); and for adenocarcinomas, the complete and overall responses were clearly superior to other histologic types when involvement was limited to the chestwall (Chi-square statistic: $p < 0.01$).

Not surprisingly, responses were found to correlate inversely with tumor volume, generally without regard to histologic type. Table 6 lists response rates stratified according to four arbitrary volume groupings for (1) all 36 evaluable patients treated with heat plus radiation and (2) the 27 evaluable patients excluding chestwall adenocarcinoma. The latter stratification was included to remove any bias associated with this highly responsive histologic tumor type/tumor location combination. Exclusion of this group did not, however, introduce a bias into volume stratification as indicated by the robust nature of the resultant mean volumes of the two groupings. When using CR rate as the strictest metric of response, a dramatic decrease in CR rate with increasing volume becomes apparent which is emphasized further by a simple linear regression fit of this data as presented in Figure 1.

An attempt was made, retrospectively, to examine the dependence of complete response rates on three hyperthermia treatment parameters (1) mean tumor temperature (2) average minimum tumor thermal dose and (3) average maximum tumor thermal dose. After re-examining the patients' thermal treatment histories, it became apparent that any correlation of response rate with mean tumor temperature would be anecdotal, at best, because of the absence of volumetric temperature profiles, and frequent occurrence of non-steady state heating; in fact,

Table 4. Histologic stratification of initial response*

	Complete	Partial	None
Radiation + heat†			
Adenocarcinoma	11/17 (65)	4/17 (24)	2/17 (11)
Squamous cell carcinoma	2/9 (22)	7/9 (78)	—
Melanoma	—	4/4 (100)	—
Fibrosarcoma	1/3 (33)	1/3 (33)	1/3 (33)
Miscellaneous	1/4 (25)	—	3/4 (75)
Total	15/37 (41)	16/37 (43)	6/37 (16)
Chemotherapy + heat			
Adenocarcinoma	—	—	1/1 (100)
Squamous cell carcinoma	—	2/3 (67)	1/3 (33)
Total	—	2/4 (50)	2/4 (50)

* Data are listed as fractions of patients treated, with percentages in parentheses; excludes unevaluable patients.

† Includes patients receiving radiation + chemotherapy.

Table 5. Initial response for the most common local tumor sites: combined therapies of radiation and heat

Site/histology	Complete (%)	Partial (%)	None (%)
Head and neck			
Sq. cell carcinoma*	2/7 (29)	5/7 (71)	
Other histologies	2/6 (33)		4/6 (67)
Chest wall			
Adenocarcinoma†	9/10 (90)	1/10 (10)	
Other histologies		3/4 (75)	1/4 (25)
All histologies	15/36 (42)	15/36 (42)	6/36 (16)

* Response rate distribution differs significantly for squamous cell carcinoma relative to other histologic types in the head and neck region (χ^2: $p < 0.01$).

† Complete response rate and response rate distribution differ significantly for chest wall adenocarcinomas compared to other histologic types in this site (χ^2: $p < 0.001$ in both cases).

Table 6. Dependence of initial response on tumor volume for local/superficial hyperthermia and radiation

Volume (cm3)*	Complete (%)	Partial (%)	None (%)
7.5 ± 2.4	6/9 (67)	2/9 (22)	1/9 (11)
7.4 ± 2.6†	3/6 (50)	2/9 (22)	1/9 (11)
19.5 ± 6.7	5/8 (63)	3/8 (37)	—
19.4 ± 7†	2/5 (60)	3/5 (60)	—
106 ± 20	3/8 (38)	4/8 (50)	1/8 (12)
100 ± 20†	1/6 (17)	4/6 (67)	1/6 (17)
540 ± 254	1/11 (9)	6/11 (55)	4/11 (36)
520 ± 280†	0/9 (0)	6/9 (67)	3/9 (33)

* Tumor sizes are divided into 4 non-overlapping groups of approximately equal patient population.

† Volume stratification excluded patients with chest wall adenocarcinoma. This sub-grouping was included to indicate a response bias due to this highly responsive tumor-site combination. Exclusion of chest wall adenocarcinomas, however, did not alter the volume stratification as evidenced by the robust nature of resultant average volume.

the latter condition renders the definition of average tumor temperature highly suspect. Before the relationship of treatment response rate to thermal dose is examined, however, it is necessary to adopt one of the many "working" definitions of thermal dose (30) in the absence of a standardized definition. In this study, to facilitate comparison with published data (8, 10, 11), 43°C equivalent minutes were used to express thermal dose. Table 7 lists a comparison of response rates with per treatment (non-site-specific) average minimum and maxium thermal dose for superficial hyperthermia and radiation. A difficulty with the interpretation of the data lies in the inclusion of chestwall adenocarcinomas in the overall response comparisons. As the tumor CR rate for this site-specific histology was nearly independent of either average minimum or maximum "measured" thermal dose, inclusion of this data introduced a definite bias in overall comparisons. This becomes evident when comparing the stratified data for all patients studied versus the subset which did not contain chestwall adenocarcinomas. Based on this subset, no distinct correlation of complete response rate with average maximum thermal dose is apparent. In addition, for average minimum thermal dose a CR rate threshold, similar to that found by Dewhirst *et al.* (8), becomes evident as illustrated in Figure 2.

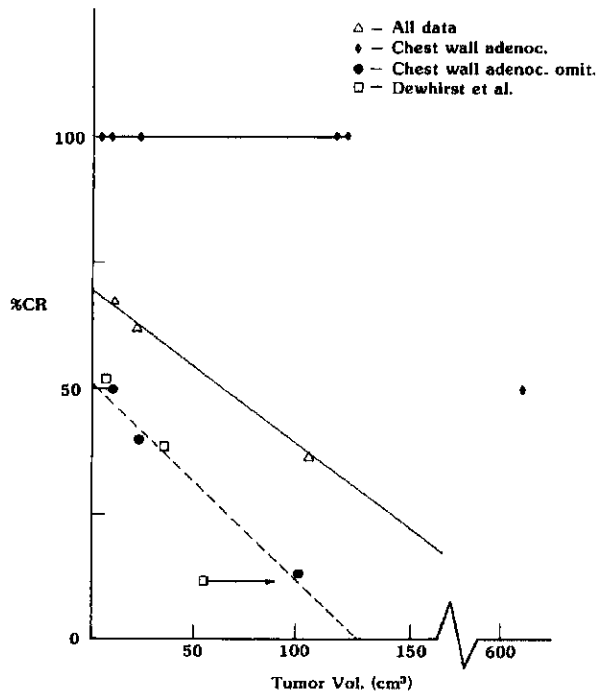

Fig. 1. Dependence of initial complete response rate on tumor volume after superficial hyperthermia and radiation. Data for complete responders were fitted by simple linear regression, as were the data excluding chest wall adenocarcinomas. The results of Dewhirst *et al.* (8) are included for comparison.

Table 7. Initial complete responses stratified by termal dose: local/superfical heat + radiation

Dose range†	All histologies (%)	Chest wall adenocarcinoma (%)	Chest wall adeno. omitted‡ (%)
	Minimum measured dose*		
0–3	3/16 (19)	2/3 (67)	1/13 (8)
3–10	3/7 (43)	4/4 (100)	0/3 (0)
10–20	2/6 (33)	1/1 (100)	1/5 (20)
>20	3/3 (100)	1/1 (100)	2/2 (100)
	Maximum measured dose§		
0–20	4/13 (31)	3/4 (75)	1/9 (11)
20–50	5/7 (56)	1/1 (100)	4/6 (67)
50–100	4/6 (67)	4/4 (100)	0/2 (0)
>100	1/6 (17)		1/6 (17)

No. of patients with evaluable thermal dose histories = 32.

* Non-site-specific average minimum thermal dose.

† Equivalent 43 C minutes.

‡ Exclusion of the highly responsive chest wall adenocarcinomas may indicate a complete response thermal dose threshold effect.

§ Non-site-specific average maximum thermal dose.

Long term response

Comparisons of long-term partial and complete response rates were examined in terms of the two most prominent response predictors, tumor volume and average minimal thermal dose, as well as for the site specific histology: chestwall adenocarcinomas. The data are presented in the form of Kaplan-Meier response duration curves in Figures 3 and 4 (11). The symbols on each plot indicate recurrences whereas the vertical bars indicate maximal followup without a change in disease status. In Figure 3, complete and partial responders were combined into four groups of statistically meaningful size. Stratified logrank methods were then applied to the grouped duration data (28).

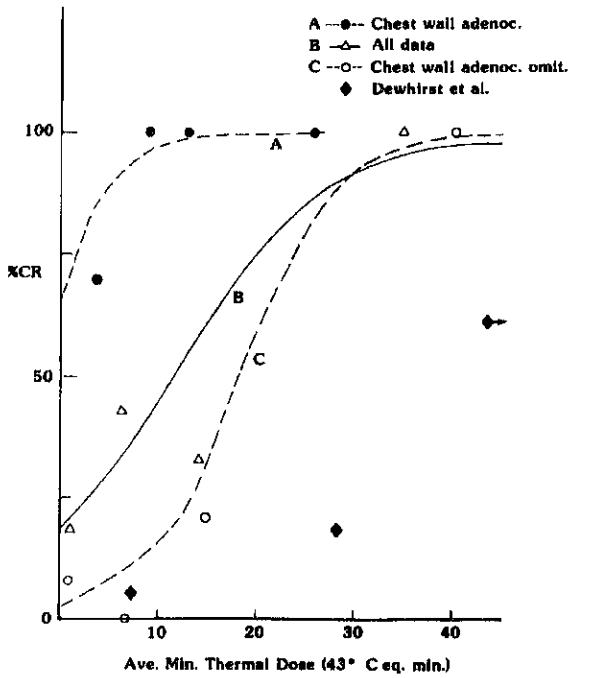

Fig. 2. Initial complete response rate for superficial therapy as a function of measured intratumor non-site specific minimum thermal dose. Curves represent logit regression fits of the functional form $\ln(P/(1-P))$ using patient response binary data and the method of Cox (7). Plotted points are for arbitrary, non-overlapping groupings of thermal dose. Data of Dewhirst *et al.* (8) are included for comparison.

Volume, which was inversely related to initial complete response, did not show a specific correlation with long-term response: logrank statistics did not indicate a statistically significant difference in the long-term response for the four volume groups examined ($p < 0.20$).

The initial response predictors of average minimum thermal dose and site specific histology, chestwall adenocarcinoma, were examined for differences in long term response when compared to the general class of complete responders. No difference was found, statistically, either for average minimum thermal dose (logrank statistic 0.10, $p = 0.77$; Wilcoxon statistic −0.43, $p = 0.66$) or for chestwall adenocarcinoma (logrank statistic 0.20, $p = 0.65$; Wilcoxon statistic 0.29, $p = 0.77$). Again, this came as a surprise at least for the former group. For the latter, however, a statistically meaningful difference, compared to all complete responders, may be masked by the lack of sufficient data, especially as the trend of the results agrees well with the findings of Scott *et al.* (31).

Also included in Figure 4, somewhat parenthetically, is the long-term response duration for patients objectively classified as partial responders. This group differed from the complete responders in that the long-term response was significantly shorter (logrank statistic 3.09, $p = 0.074$; Wilcoxon statistic 2.53, $p = 0.014$). This was also supported by a difference in mean time to recurrence of 3.4 months for PR's vs. 9.4 months for CR's.

Toxicity

Six percent of the administered local/superficial hyperthermia treatments resulted in thermal injury to patients. On a per patient basis, this amounted to a 40% injury rate. The severity of the injuries is outlined in Table 8. No significant correlation could be made with observed indicated average minimum or maximum thermal dose to the tumor, or with observed single session maximum skin temperature or thermal dose. The lack of correlation with the latter two quantities is not surprising, however, in view of (a) difficulties in accurately measuring unmodulated skin temperatures and (b) insufficient temperature monitoring to ascertain location(s) of hot spot(s). Although tissue eventually regenerated in all patients with the exception of a single patient with a third-degree burn (resulting in the destruction of ear cartilage), an induced sensitivity to heat frequently accompanied thermal injury which often limited the effectiveness of subsequent hyperthermia treatments.

DISCUSSION

Initial tumor response

Probably the most consistent of all reported predictors of the initial tumor complete response rate for heat combined with radiation, irrespective of heating technique, is

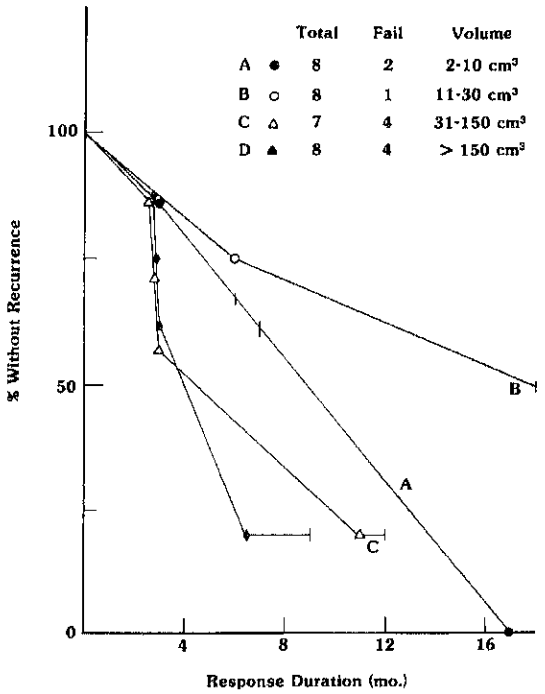

Fig. 3. Long-term response to superficial hyperthermia and radiation as a function of tumor volume. Stratification groupings were of approximately equal size and include partial as well as complete responders. No statistically significant difference in response could be shown between groups (logrank $p < 0.20$). Vertical bar indicates the limit of follow-up for a patient without recurrence of disease.

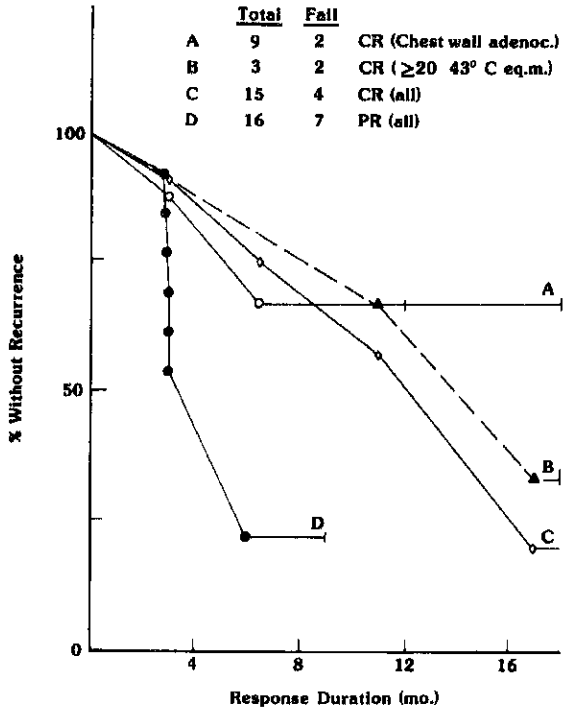

Fig. 4. Long term response duration for the four most significant treatment subcategories: (A) complete response, chest wall adenocarcinomas; (B) all tumor types with minimum thermal dose greater than threshold (>20, 43°C eq. m.); (C) all tumor types with complete response; (D) all partial responders. No statistically significant difference was observed among the subclasses of complete responders: (A) vs (C) logrank statistic, 0.17, $p = 0.77$; Wilcoxan statistic, 0.58, $p = 0.77$); and (B) vs (C) (logrank statistic, 0.10, $p = 0.77$; Wilcoxan statistic, 0.58, $p = 0.56$). Significant improvement in the duration of response was observed between complete and partial responders (C) vs. (D) (logrank statistic, 2.53; $p = 0.014$).

the inverse relationship to tumor volume (8, 9, 11, 25, 26, 33, 37). As Table 6 and Figure 1 illustrate, our results confirm this finding. As a comparison, the findings of a study by Dewhirst *et al.* (8) have been included in Figure 1, with the volume-response data taken for the same heat fractionation scheme (twice weekly) and total radiation doses (on the order of 30–40 Gy). The marked similarity between the results of the two studies strongly suggests the following: when hyperthermia is employed with moderate doses of radiation for metastatic and recurrent neoplasms, superior complete response rates (CR_{50} or greater) can be reliably predicted only for relatively small tumors when using presently available techniques and methodologies.

Table 8. Toxicity

Mode	Frequency of side effects*	Complications/injuries	No. of patients
		Burns	
Local hyperthermia	17/42 (40%)	1. 1st deg.	1
		2. 2nd deg. blistering	14
		3. 3rd deg. necrosis	1
		Edema and erythema	1

* Per patient side effect frequency.

Consistent with the observations of other investigators (6, 10, 22, 25, 26), our findings support the conclusion that, for both overall and complete response rates, tumor histologic characteristics, by themselves, are not a reliable predictor of initial response. It does appear, however, that a definite site-histologic type correlation exists for adenocarcinomas (Fig. 1): when involvement was limited to the chestwall, the complete and partial response rates were clearly superior to the general class of tumors treated (chi squared p 0.01 for both); such a superior response is consistent with earlier findings (6, 26, 31, 33). What proved to be surprising, however, was the finding that the complete response rate remained high for very large areas of involvement (larger than 15×15 cm^2) where heating was considered inadequate: similar heating conditions produced inferior responses for other tumor types in the same location.

The hyperthermia parameters of average minimum thermal dose (9, 10) and average tumor temperature (37) have been previously reported as important complete response predictors. Unfortunately, only the former correlation could be examined in this study, due to insufficiencies in the hyperthermia treatment data, as previously mentioned. Although the data indicate a relationship between increasing response rate and increasing non-site-specific average thermal dose, when expressed in terms of 43°C eq. min., the form of the relationship is distorted because of the large proportion of highly responsive chestwall adenocarcinomas. With this component removed from the data, a complete response threshold, similar to that found by Dewhirst *et al.* (8), appears to be in evidence when presented in Figure 2, curve C, although this should be qualified in light of the limited amount of data (see Table 7). The calculated curves are maximum-likelihood (7) best fits to the logit of the patient complete response data. For an initial complete response rate greater than CR_{50}, it appears that an average minimum tumor dose threshold of twenty to thirty 43°C eq. min. must be exceeded, if radiation doses of 20 to 40 Gy are used in conjunction with the heat. Although this is a factor of approximately two smaller than the threshold suggested by the data of Dewhirst *et al.* (8) (included in Fig. 2), no significance to this disparity should be inferred considering the small number of patients, in this study, that received large average minimum thermal doses.

Long term response

Unfortunately, the lack of positive long-term correlation of complete response with any response predictors, especially with tumor average minimum thermal dose, was quite disappointing. The results of Dewhirst *et al.* (11) point to a strong, positive long-term response correlation with increasing minimum thermal dose. Our nonconfirmation of this correlation was, at first glance, very

perplexing especially for the smallest tumor volume group for which heating reproducibility and average minimum thermal dose was highest. However, as was pointed out by Dewhirst *et al.* (11), consideration of minimal thermal dose in the absence of a quantitative measure of tumor volume fraction heated to this dose, is too simplistic to be reliable as a long-term response predictor. Crude volumetric temperature estimates (using the 2-dimensional tumor thermal mapping data and calculated microwave applicator heating patterns) of the neoplasms treated in this study indicates that a substantial tumor volume fraction (greater than 20%) was at or below the estimated complete response threshold of approximately twenty to thirty 43°C equiv. min. in all but a few instances, small tumors included. Thus, we conclude that lack of long-term response correlation was probably caused by inadequate tumor heating as characterized by the presence of large thermal gradients during heating concomitant with large volume fractions receiving thermal doses at or below the estimated dose response threshold. This serves to illustrate the chief difficulty with most non-invasive microwave hyperthermia treatments: large thermal gradients and inadequate thermal dose delivery is the rule rather than the exception.

Increasing hyperthermia effectiveness

The vexing problem of inadequate tumor heating, encountered repeatedly in this study, will remain virtually insoluble without a significant alteration in non-invasive microwave equipment and techniques. A possible solution suggests itself through a logical extension of present technology: commercial development of multi-element focused arrays (15) and multi-element microstrip antennae (13, 35). The important advantage of these multi-element arrays will be the ability to control RF power and phase independently and thus effectively "tailor" the applicators to anatomical sites as well as irregularly defined neoplasms.

However, even with such improvements in tumor heat delivery capabilities, practical limitations to the adequate heating of a tumor bulk will inevitably exist. What is considered "adequate heating" for long-term control? The answer must be related to the total tumor cell reduction factor achievable by radiation plus hyperthermia. If a reduction of between 10^{-10} and 10^{-12} in cell survival is required for effective long-term control of neoplasms, as suggested by Oleson *et al.* (25), it may be propitious to look elsewhere for techniques to augment inadequate heating by increasing cellular thermal sensitivity at temperatures (or thermal doses) which are not presently therapeutically effective. Stewart *et al.* (34) have pointed out two such techniques: temperature (17) and pharmacologic (1, 38, 39) manipulation of heat sensitivity. The former requires short-term tumor temperature elevation beyond 43°C, followed by long-term exposures at temperatures $\leq$ 41°C. Unfortunately, this step down heating sensitization technique suffers from the basic problem it is trying to address: the frequent inability to achieve a temperature of 43°C within a sufficient volume of tumor. Pharmacologic manipulation, on the other hand, may hold the most promise for effective heat sensitization. In addition to electron-affinic radiosensitizers (1) and local anesthetics (38, 39), agents which can produce modestly lowered cellular pH (between a pH of 6.5 and 7), such as glucose (12), may have the potential to increase heat sensitivity by as much as three orders of magnitude especially at temperatures $\leq$ 42.5°C (30). Such increased sensitivity may lead to the increased effectiveness of hyperthermia treatments and may also allow for a reduction in the temperature required for therapeutic benefit, thus making hyperthermia significantly more tolerable to heat sensitive patients.

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