The Clinical Efficacy of Localized Hyperthermia

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Abstract

Localized hyperthermia alone can induce regressions in human neoplasms, but superior results can be obtained by integrating hyperthermia with even low doses of radiotherapy. Several clinical trials demonstrate that hyperthermia plus irradiation can produce higher tumor response rates than the same irradiation alone. While minimal enhancement of irradiation effects on normal tissues is reported, this may be due in part to the physical localization of the heating preferentially in tumors, often assisted by normal tissue cooling or shielding. These advantages may exist only in special circumstances in the treatment of deep tumor volumes. A variety of hyperthermia and irradiation fractionation schemes has been used; the optimal one(s) is yet to be clearly established. To date, no tumor histology has been shown to be more sensitive than another, although the relative radiosensitivity of melanomas, especially to smaller fraction sizes, is substantially offset by the addition of hyperthermia. Larger tumor volumes are more difficult to heat and achieve lower response rates, but may be relatively less problematic for combined hyperthermia and irradiation than for irradiation alone. Currently used microwave and unfocused ultrasound applicators, when used singly, usually achieve potentially therapeutic temperatures to only about 2- to 4-cm depth, although site-specific tissue characteristics may greatly alter this in individual circumstances. Anatomical factors limit the number of sites which can be usefully treated because of inflexibilities of the currently available equipment. Single-point temperature measurements during treatment correlate poorly with tumor response, while minimum mean tumor temperatures may correlate more strongly. Local and radicular pain occurs commonly during treatment, superficial burns occur occasionally, but major tissue complications have been reported rarely. While the efficacy of localized hyperthermia in augmenting tumor responses to irradiation with acceptable toxicity is established, much important clinical work remains to be done in carefully defined treatment protocols.

Introduction

Methods to induce localized hyperthermia from external electromagnetic and ultrasonic wave sources have been rapidly improving. The clinical work begun at Stanford in 1977 using ultrasound transducers, and later microwave waveguide applicators, was limited to the treatment of quite small superficial neoplasms (31). Applicators with effective field diameters up to 10 cm are currently available (34), and arrays of ultrasound and of microwave applicators are now being developed with the objectives of providing broader subsurface field sizes, segmental control of applicator power output, greater temperature homogeneity, flexibility in application, and comfort to the patient.

While the clinical results obtained using the currently available technology inevitably fall short of the results eventually possible, insights into the responses of human tumors to localized hyperthermia are becoming apparent, especially when thermal dosimetry measures can verify that the treated tumors received hyperthermia fairly homogeneously. However, comparative analyses of response rates according to histology, fractionation scheme, tumor size and site, blood flow rates, etc., all require a quantified comparison of the heat "doses" given, involving both biological and physical considerations of the temporal and across-tumor temperature variations which invariably exist. Much of the clinical data accumulated to date lack sufficient thermal dosimetry information to allow such careful dose comparisons, and many conclusions based on these clinical observations must be qualified by this consideration. This discussion serves to define some of the findings and many of the limitations in the current clinical work with localized hyperthermia, as well as to suggest a few needed directions of investigation based upon these findings and limitations.

Hyperthermia Alone

Marmor et al. (30, 31) reported on ultrasound-induced hyperthermia for selected small, superficial neoplasms (<4 cm in diameter, <3 cm deep). Thermometry studies documented that temperatures typically varied ±1° across the tumor volumes; greater variation could be seen at different tumor depths, especially over bone, although not always. Center tumor temperature of 43-45° was maintained for 30 min in each session, and repeated 3 times/week for a total of 6 sessions. Additional treatments were sometimes given if partial response had occurred. Of 44 evaluable courses, 5 induced complete and 14 induced partial tumor regressions (Table 1). The median duration of response was only 6 weeks. Pain during treatment was the most common adverse effect (Table 6). A few patients developed superficial blisters, healing quickly. No special problems developed in heavily irradiated sites (28). Similar results using similar ultrasound equipment have been obtained by Corry et al. (11), by others using electromagnetic equipment (1, 19, 26, 27, 40, 42).

These response rates verify the antineoplastic activity of hyperthermia in human tumors but are inferior to those achieved by Marmor and Hahn (28, 29), Corry et al. (12), and others (1, 8, 9, 15, 18, 21, 26, 39, 41, 42) with hyperthermia combined with low- to moderate-dose irradiation. Corry et al. (11, 12) achieved CRs in 13 of 21 lesions (62%) with hyperthermia (43.5° ± 0.5° at tumor center for 1 hr) followed by irradiation (400-rad fractions, 3 days/week to 2400 to 4000 rads total). Second lesions in 10 of these patients received similar hyperthermia treatments alone; only one complete response was obtained. A similar study by U et al. (42), outlined in Tables 1 to 4, achieved CRs in 6 of 7 evaluable lesions after heat plus irradiation (<2000 rads in 5), but none after heat alone. No significant normal tissue toxicity...
occurred in either group. Marmor and Hahn (28) reported on 16 patients with tumors recurrent after irradiation. Of 6 sites previously treated to 4000 to 6000 rads, an additional 1200 to 2400 rads plus hyperthermia (as described above) were delivered with no or minor skin toxicity, and with 5 of the 6 courses inducing CRs. The safety and superior efficacy of such combined therapy seem to be generally acknowledged now; few clinical reports on the use of hyperthermia alone have recently appeared.

Hyperthermia and Irradiation

Comparative Trials of Irradiation versus Irradiation plus Hyperthermia

Tumor Response. In patients with similar superficial lesions, the responses to irradiation or the same irradiation plus hyperthermia are shown in Table 2. In most cases, each patient had 2 or more tumors, allowing a response comparison to be made for each patient (“same patient comparisons”). Only the small series by Marmor and Hahn (29) reports using a blind method of randomization. In each study, the response rates to irradiation alone were markedly improved by the addition of hyperthermia.

In obtaining these results, the irradiation was delivered using a variety of fraction sizes, fractionation intervals, and total doses (Table 3). A wide range of equipment and application methods was used. Some studies used radiotherapy immediately before hyperthermia, others immediately after, and Marmor and Hahn (29) used radiotherapy after 15 min of each 45-min heating session. Some used hyperthermia with every radiotherapy fraction, some used it less often, and the total number of hyperthermia treatments varied from 2 to 13. Different temperatures were applied for different durations, and few studies reported temperature distributions through the tumor volumes. It is surprising that similar tumor response enhancement ratios were obtained despite these many variations. However, extensive experimental work on each of these parameters suggests that many are likely to show clinical significance with greater scrutiny (17).

Marmor and Hahn (29), Kim et al. (20), and Scott et al. (3) comment that the tumor responses seen following combined hyperthermia and radiotherapy were often faster than those seen after radiotherapy alone. Scott et al. (3) have shown that the

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Table 1

Responses of superficial tumors to hyperthermia alone

<table>
<thead>
<tr>
<th>Institution</th>
<th>Ref.</th>
<th>Hyperthermia method (MHz)</th>
<th>Prescribed Temp. x time</th>
<th>No. of treatments</th>
<th>No. of evaluable patients</th>
<th>CR (%)</th>
<th>Partial response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Arizona</td>
<td>Manning et al. (27)</td>
<td>MW (915, 2450)</td>
<td>42.5-44° x 40 min</td>
<td>2-22</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>University of California</td>
<td>Luk et al. (26)</td>
<td>MW (915, 2450)</td>
<td>42.5° x 60 min</td>
<td>5-12</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duke University</td>
<td>U et al. (42)</td>
<td>MW (915, 2450)</td>
<td>42-44° x 40-50 min</td>
<td>2-9</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Kyoto University</td>
<td>Abe et al. (1)</td>
<td>RF capacitive (13.56)</td>
<td>41-46° x 30-60 min</td>
<td>4-9</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>M. D. Anderson</td>
<td>Corry et al. (11)</td>
<td>US (1-3)</td>
<td>43-50° x 60 min</td>
<td>6-12</td>
<td>28</td>
<td>5 (18)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Memorial Hospital</td>
<td>Kim and Hahn (19)</td>
<td>RF inductive (27.12)</td>
<td>41-45.5° x 30-40 min</td>
<td>2-9</td>
<td>19</td>
<td>4 (21)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Marmor et al. (30)</td>
<td>US (1-3)</td>
<td>43-45° x 30 min</td>
<td>6</td>
<td>44</td>
<td>5 (11)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Washington University</td>
<td>Perez et al. (40)</td>
<td>MW (915)</td>
<td>41-43° x 60-80 min</td>
<td>NS</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Total 131 19 (15) 42 (32)

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Table 2

Responses of superficial lesions to irradiation and irradiation plus hyperthermia

<table>
<thead>
<tr>
<th>Institution</th>
<th>Ref.</th>
<th>No. of evaluable patients (trials)</th>
<th>Same patient comparisons</th>
<th>CR within 1 mo</th>
<th>CR during follow-up</th>
<th>CR for 2 mo</th>
<th>% of irradiation alone</th>
<th>% of irradiation plus hyperthermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke University</td>
<td>U et al. (42)</td>
<td>7</td>
<td>7</td>
<td>CR</td>
<td>14</td>
<td>86</td>
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<tr>
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<td>86</td>
<td>59</td>
<td>CR</td>
<td>33</td>
<td>80</td>
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<tr>
<td>M. D. Anderson</td>
<td>Corry et al. (12)</td>
<td>18</td>
<td>21</td>
<td>CR</td>
<td>0</td>
<td>62</td>
<td></td>
<td></td>
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<tr>
<td>IMRS (Rome)</td>
<td>I</td>
<td>Arcangeli et al. (8, 7)</td>
<td>26</td>
<td>CR</td>
<td>42</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>17</td>
<td>17</td>
<td>CR</td>
<td>35</td>
<td>64, 78*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>16</td>
<td>16</td>
<td>CR</td>
<td>37.5</td>
<td>67, 77*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
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<td>CR</td>
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<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Roswell Park</td>
<td>Scott et al. (3)</td>
<td>31</td>
<td>CR</td>
<td>39</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanford University</td>
<td>Marmor and Hahn (29)</td>
<td>15</td>
<td>15</td>
<td>CR versus PR*</td>
<td>7</td>
<td>47</td>
<td></td>
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</tbody>
</table>

Total 231 (234) 196

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* MW, microwave; RF, radio frequency; US, ultrasound; NS, not specified.
improved initial response rate can be durable. Treating paired lesions in 31 patients with radiotherapy with or without hyperthermia (described in Table 3), they obtained CRs following combined treatment versus radiotherapy alone in 32% versus 10% at the end of treatment (31 evaluable patients), 87% versus 39% at 6 months (31 evaluable patients), and 100% versus 53% at 1 year (19 evaluable patients) (at 1 year, p < 0.001).

**Normal Tissue Damage.** Several of these comparative studies report that the normal tissue damage incurred in the combined therapy sites was not significantly greater than that in the radiotherapy-alone sites (20, 23, 42). Some of the trials used relatively low irradiation doses, as low as 1800 rads, which would not be expected to induce skin reactions even if modest enhancement of irradiation effect by hyperthermia had occurred. However, Kim et al. (20) used 4 fractionation schedules with large time, dose, and fractionation (i.e., Ellis equivalent nominal standard dose) values, 81 to 94, to treat melanoma lesions. In adding hyperthermia (Table 3) to second lesions in each patient, they observed no enhancement of irradiation damage. Mean tumor temperatures were 1–1.5° higher than mean normal tissue temperatures. Scott et al., in the trial described above, found the combined therapy sites to be "essentially indistinguishable" from the radiotherapy-alone sites at the end of therapy and 6, 12, 18, and 24 months later. Skin cooling had been provided. Corry et al. (12) observed acute (in 3 to 6 days), transient local edema and tenderness in all of 21 lesions treated with hyperthermia and 400-rad fractions.

Greater skin reactions have been noted in combined therapy than in radiotherapy-alone areas by Marmor and Hahn (29) and have been systematically studied by Arcangeli et al. (6, 7). In one of his protocols, paired lesions were treated at 42.5° (lesion base) for 45 min immediately after 500-rad fractions twice per week to 4000 rads total. Skin cooling had not been provided. The incidence of moist desquamation was 1.78-fold greater in combined therapy than in radiotherapy-alone sites. However, this was less than the improvement in the complete tumor control rate, as will be discussed next.

**Therapeutic Gain.** In some of these trials, the irradiations used were high-energy photons which could provide a skin-sparing effect (Table 4). All trials found that the hyperthermia method used could provide greater tumor than normal tissue heating, which was attributed to the energy deposition characteristics of the applicators, active skin cooling, or the tumor tissue absorption or vascular properties involved. Thus, the improved tumor responses with minimal normal tissue damage do not necessarily imply that the tumors were more sensitive to heat, but perhaps only that the hyperthermia (and sometimes the radiotherapy) could be physically localized preferentially in tumors.

In adding radiofrequency or microwave hyperthermia to irradiation in 4 different fractionation regimens outlined in Table 3, Arcangeli et al. (4, 6) showed enhancement ratios to be consistently superior in tumors (based on CR rates) than in skin (based on moist desquamation rates). This remained true whether 150- to 200- or 500- to 600-rad fractions were used, and whether hyperthermia immediately followed or was delayed 4 hr after radiotherapy. Not surprisingly, the greatest therapeutic advantage was seen when skin was actively cooled while tumors received high-temperature (45° at tumor depth for 30 min) hyperthermia.
perthermia. Substantial enhancement in the incidence of skin desquamation occurred when hyperthermia immediately followed 500-rad fractions compared to the same irradiation alone (64% versus 36%), but was improved by delaying hyperthermia 4 hr after radiotherapy (46%). Such studies can provide valuable suggestions about the relative benefits of different treatment regimens. However, since the relative skin and tumor temperatures may differ greatly with the applicators used (and were not separately monitored here), such calculations of therapeutic gain depend entirely on the characteristics of the equipment used, the lesions treated, and the techniques of application used. Also, given the absorption variations that may exist between different tumors and between different anatomical sites, such estimates may be greatly modified by the tumor and normal tissue characteristics involved in each treatment. Additional considerations are discussed by Gillette (16) in this volume.

Danger exists in extrapolating the results obtained with superficial lesions to the results potentially obtainable in deep tumor volumes. In the latter, substantial irradiation doses may be delivered to the surrounding tissues despite careful treatment planning. Deep-heating techniques, particularly with electromagnetic methods, often produce poorly localized or regional heating. Further, visceral tissues may have quite different thermal sensitivities than superficial tissues. Without the physical localization advantages which exist for superficial lesions, it cannot be assumed that similarly efficacious and safe results can be obtained for deep tumor volumes.

Factors Potentially Influencing Treatment Results

Tumor Histology. The responses of specific tumor histologies in selected series using hyperthermia alone or in combination with radiation therapy are reported in Table 5, and the response of each histology is compared to the overall response rate for that series. All told, protocols using hyperthermia alone or in combination with radiotherapy have not consistently shown any tumor histology to be more responsive than any other. The irradiation doses often varied within each series, and compensations for histologies known to be more radioreistant may in part explain the homogeneity of the responses. Only the clinical series by Bicher et al. (10) used an identical treatment course for all histologies, one which emphasized hyperthermia (4 treatments at 45°for 90 min, twice per week, then one week rest; last, four 400-rad fractions plus 42°for 90 min, twice per week).

In a multivariate analysis of the tumor responses in 163 patients treated with a variety of hyperthermia techniques, Olson et al. (38) found no correlation between tumor response rates and histologies. This contrasts strongly with the large variations in radiation sensitivities known to exist between different histologies. Yet variations in thermal sensitivities are known to exist between different experimental cell lines receiving highly controlled thermal exposures (17), and further clinical experience may be more enlightening.

In treating superficial melanoma lesions with 200-, 330-, 400-, 550-, or 660-rad fractions to similar total doses (3850 to 4290 for groups >200 rads), Kim et al. (20) showed that tumor control rates were improved by adding hyperthermia to each of the fraction sizes. Lesions receiving 200- to 400-rad fractions had control in only 7 of 28 (25%) with irradiation alone, but in 9 of 16 (56%) with the addition of hyperthermia (Table 3), similar to the response with 550- to 660-rad fractions alone (19 of 35; 54%). Thus, the benefit of large fraction sizes alone was equaled by the addition of hyperthermia to smaller fraction sizes. Lesions that received the larger fractions (with higher time, dose, and fractionation) plus hyperthermia had an even higher response rate (22 of 23; 76%). Other series indicate that the relative radiosensitivity of melanomas is substantially overcome by the addition of hyperthermia, making them similar in response to other tumors (9, 12, 40, 43).

Tumor Volume. Larger tumors may have relatively greater poorly perfused, hypoxic, and acidic cell populations which would have greater sensitivity to hyperthermia, or heat to higher temperatures during treatment. On the other hand, larger volumes may be more difficult to heat homogeneously. Dewhirst et al. (13) treated 130 spontaneous large animal tumors with irradiation alone or with hyperthermia in a prospectively randomized trial. Large tumor volumes (>100 cu cm) responded more poorly than smaller volumes to combined therapy (33% versus 72% CR). However, tumors 20 to 100 cu cm responded nearly as well as tumors <20 cm to combined therapy (56% versus 73% CR), but far more poorly to irradiation alone (9% versus 69% CR). This indicates that larger tumor volumes were more difficult to treat by both irradiation and irradiation plus heat, although less so for the latter.

Kim et al. (20) treated 108 melanomas in 38 patients with irradiation with or without inductive hyperthermia (described in Table 3), and reported that tumor volumes >10 cu cm achieved nearly the same tumor control rates as those <10 cu cm (65% versus 73%) with combined therapy, but had distinctly poorer

<table>
<thead>
<tr>
<th>Institution</th>
<th>No. of evaluative patients (sites)</th>
<th>Response criteria</th>
<th>All histologies (%)</th>
<th>Adenocarcinoma*</th>
<th>Squamous cell carcinoma*</th>
<th>Mela- nomas*</th>
<th>Lym- phomas b</th>
<th>Sar- comas*</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. D. Anderson</td>
<td>28</td>
<td>CR + PR c</td>
<td>18/28 (64)</td>
<td>3/5 (60)</td>
<td>3/5 (61)</td>
<td>5/10 (50)</td>
<td>3/7 (43)</td>
<td>5/11 (45)</td>
</tr>
<tr>
<td>Memorial Hospital</td>
<td>19</td>
<td>CR + PR</td>
<td>10/19 (53)</td>
<td>0/1</td>
<td>4/6 (67)</td>
<td>5/10 (50)</td>
<td>1/1</td>
<td></td>
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<tr>
<td>Stanford University</td>
<td>24</td>
<td>CR + PR</td>
<td>19/44 (43)</td>
<td>3/9 (33)</td>
<td>10/18 (56)</td>
<td>1/4</td>
<td>3/6 (50)</td>
<td>1/4</td>
</tr>
<tr>
<td>M. D. Anderson</td>
<td>21</td>
<td>CR</td>
<td>13/21 (62)</td>
<td>4/7 (57)</td>
<td>1/1</td>
<td>7/11 (64)</td>
<td>1/2</td>
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<tr>
<td>Memorial Hospital</td>
<td>86</td>
<td>CR</td>
<td>69/86 (80)</td>
<td>9/10 (90)</td>
<td>31/38 (81)</td>
<td>17/21 (81)</td>
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<tr>
<td>Kim et al. (21)</td>
<td>41</td>
<td>CR</td>
<td>33/44 (75)</td>
<td>7/8 (88)</td>
<td>3/5 (60)</td>
<td>17/29 (59)</td>
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<td>Henry Ford Hospital</td>
<td>62</td>
<td>CR</td>
<td>49/82 (61)</td>
<td>24/33 (73)</td>
<td>7/9 (78)</td>
<td>8/7 (53)</td>
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<tr>
<td>Washington University</td>
<td>94</td>
<td>CR</td>
<td>55/94 (58)</td>
<td>16/30 (53)</td>
<td>20/39 (51)</td>
<td>16/22 (73)</td>
<td>3/3</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, ratio of response rate for specific histology to response rate for all histologies in that series.

b Includes Mycosis fungoides.

c PR, partial response.
Localized Hyperthermia

control rates (19% versus 58%) with radiation therapy alone.

Oleson et al. (38), in the multivariate evaluation described above, showed that larger tumor volumes had a significant negative correlation with response rate. Importantly, these volumes were in turn correlated with lower minimum tumor temperatures (and with higher maximum tumor temperatures).

These studies suggest that larger tumor volumes can be a negative factor for hyperthermia plus irradiation, but a less negative one than for irradiation alone. In the combined therapy trials, greater intratumoral thermal gradients in larger tumors (with lower minimum temperatures) seem to account for some of this negativity, and might be offset if they can be minimized by improved treatment methods.

Tumor Depth. Perez et al. (39, 40) reported on 101 superficial tumors treated with irradiation and hyperthermia, most with 915-MHz microwaves from single waveguide applicators. Average temperatures at the depths of the tumors (central axis) were >42.5° in 29 of 43 (67%) tumors ≤2 cm deep and 24 of 37 (65%) tumors 2.1 to 4 cm deep, but in only 4 of 11 (36%) tumors >4 cm deep. This poorer ability to heat tumors >4 cm deep translated into poorer response; 41 of 80 (51%) tumors ≤4 cm deep had complete response versus 3 of 11 (27%) tumors >4 cm deep. Similar effective depth penetration is achieved by single unfocused ultrasound transducers (31). Given the biophysical characteristics of microwaves and ultrasound waves, one would anticipate that multiple and/or focused sources, either fixed or scanning, or lower frequency electromagnetic techniques would be required to achieve significantly greater effective penetration (17).

Radiation Dose. While increased response rates with higher irradiation doses can only be expected, of concern is what minimum doses combined with hyperthermia are necessary to achieve frequent complete responses in sites irradiated previously. This would be expected to involve the “dose” of hyperthermia given as well.

In patients with epidermoid carcinomas of the head and neck or adenocarcinomas in the series of Perez (Ref. 40, described above), only 2 of 15 (13%) responded completely when fewer than 8 treatments (3200 rads plus heat) were given, while 33 of 50 (66%) responded completely when 8 to 10 treatments (3200 to 4000 rads plus heat) were given. Partial response rates also increased from 7 to 30%. Melanomas responded well even at low irradiation doses combined with hyperthermia, with 1000 to 2000 rads plus heat inducing 4 of 6 complete and 2 of 6 partial responses.

Scott et al. (41) reported the results of the RTOG 77-10 trial which randomized lesions (multiple in the same patient) to 500 rads plus hyperthermia (Lesion 1), 700 rads alone (Lesion 2), or 800 rads alone (Lesion 3); treatments were given at 72-hr intervals. Hyperthermia generally was 43–44° at the tumor center using 915-MHz microwaves. Only 3 treatments were given (1500, 2100, and 2400 rads, respectively). At the end of treatment, 11 of 12 (91%) Lesion 1, 7 of 12 (58%) Lesion 2, and 8 of 12 (67%) Lesion 3 had completely or partially responded. Superior CR rates were noted 3 months after treatment in the combined therapy Lesion 1 (8 of 8; 100%) compared to Lesions 2 (2 of 8; 25%) and 3 (5 of 8; 63%).

In the series by Bicher et al. (10) discussed above, total responses were obtained in 49 of 82 (60%) lesions and partial responses in 27 of 82 (33%), when only four 400-rad fractions were integrated with 8 hyperthermia treatments. Most other clinical studies used widely varying irradiation doses without analyzing their response rates according to them. The results of treatment will inevitably be tied to the factors affecting tumor response to hyperthermia as well, and these may need to be better quantified before the irradiation doses necessary for complete and lasting responses can be defined.

Hyperthermia Temperature. In assessing tumor responses in terms of single point (tumor center) average temperatures using hyperthermia alone (described above), Marmor et al. (31) found no differences in the response rates after 43.0–43.5° (5 of 9, 56%), 44.0–44.5° (7 of 12, 58%) or 45.0° (2 of 5; 40%). Also, there were no differences in the incidences of burns, extensive necrosis, or induction of pain. This work using ultrasound equipment was similar to work done by Corry et al. (11, 12). They also found no differences in the response rates for single-point measurements (tumor center) between 43 and 44° (8 of 15; 53%) and 45 and 47° (3 of 7; 43%).

In using primarily 915-MHz microwave equipment, Perez et al. (40) reported temperatures (at tumor depth, central axis) versus response rates. Rates did not differ for temperatures between 41° and 42° (12 of 22; 55% CR) and >42.5° (32 of 57; 56% CR). Temperatures <41° had lower responses (4 of 12; 33% CR). These studies indicate that there is little correlation between single-point temperature measurements in the range of about 41–47° and the probability of tumor response.

In their multivariate analysis, Oleson et al. (38) found minimum tumor temperatures to be the overall most important variable in predicting CR. There was no significant correlation between response and maximum tumor temperature in the interstitially treated patients, where thermal dosimetry was the most extensive. This confirms the prior work of Dewhirst et al. (13) in large animal spontaneous tumors. It is obvious that single-point tumor temperatures are not representative of tumor temperature distributions, and it appears that minimum tumor temperatures are more strongly correlated with response than are tumor maximum or core temperatures.

Little clinical comparative data exist on the number of hyperthermia treatments necessary to obtain a significant enhancement of an antitumor irradiation effect. Work by Arcangeli et al. (6, 7) (Tables 2 and 3, protocol II) suggests a small benefit of 10 over 5 hyperthermia treatments; 17 patients with multiple lesions received 5000 rads over 5 weeks alone to one lesion and the same irradiation plus hyperthermia either once or twice weekly to second or third lesions. Similar CR rates were achieved at the end of therapy for 10 and 5 heat treatments (7 of 9, 78%; 9 of 14, 64%, respectively), both greater than for irradiation alone (6 of 17; 35%). But by 8 months, fewer total failures had occurred after 10 than 5 treatments (22% versus 43%), which suggested a treatment superiority to the authors. Larger patient numbers are needed to confirm this result.

Toxicity. Apart from the enhancement of irradiation effects, acute toxicities have been attributed to hyperthermia (Table 6) because they occurred as the treatment power was applied, or appeared typical of heat damage (vesicles, burns). Late toxicities have generally not been reported, perhaps in part because of the limited longevity of the treated patients. A recent large animal study (32) suggests that the pathologically graded level of acute damage (at 24 hr) can be a poor predictor of the level of late damage (at 1 month) after treatment ≥46° for 30 min.

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4749s
Hyperthermia and Chemotherapy

The synergistic or additive enhancement of certain chemotherapies by hyperthermia has been demonstrated experimentally (17), and offers the possibility of locally potentiating their effects in tumor masses. Little meaningful clinical experience has been reported yet, and such treatments deserve investigation in controlled protocol studies.

Fairman (14) reported 22 cases of carcinoma of the head and neck treated with Adriamycin and bleomycin, and microwave hyperthermia (2450 MHz) for 1 hr, 3 times/week at the initiation of each cycle. Temperatures were not monitored; 11 cases received radiotherapy in addition. In this uncontrolled trial, 21 of 22 (85%) cases showed partial or complete responses. In one case, a Hodgkin’s disease tumor mass previously resistant to these combined drugs showed regression and necrosis when hyperthermia was added to them.

Moffat et al. (35) reported on 14 patients with tumors of the head and neck treated with various chemotherapeutic agents, most often methotrexate, and capacitive radiofrequency hyperthermia (13.56 MHz). Single point temperature measurements summed for the 13 of 14 patients monitored were reported and mostly ranged between 41.5–43°C for sessions lasting 72 to 120 min. Three consecutive daily sessions were integrated with each chemotherapy cycle, given every 3 to 6 weeks, for an average of 3 cycles (range, 2 to 11 cycles). In this uncontrolled trial, 3 of 6 patients surviving for 21 to 55 weeks responded, 2 completely and one partially, and 3 of 8 deceased patients had initially responded partially. Of note, 3 of 5 patients previously unresponsive to methotrexate responded to it when hyperthermia was added (2 partially and one completely, lasting for at least 21 weeks).

Future Directions

The accessibility of superficial lesions to localized hyperthermia, sometimes allowing relatively homogeneous heating, thorough temperature measurement, easy assessment of response, and the potential for introducing treatment-modifying agents, makes possible the investigation of many critical questions. Laboratory insights into the optimum sequencing and frequency of irradiation and hyperthermia, with or without a delay interval between them, remain largely without clinical verification. For instance, recent investigations indicate that tolerability may persist for several days (44) and may affect radiosensitization (36). If a decaying efficacy of hyperthermia treatments is observed clinically, then the minimum number of treatments needed to obtain a substantial irradiation enhancement needs to be defined.

Treatment modifiers may have a substantial impact on treatment delivery and tumor response. Methods have been suggested to increase power absorption in tumors, such as by the injection of absorption-enhancing agents; to increase heating in tumors above that in normal tissues, such as by the administration of drug vascular modifiers; and to enhance cellular response, such as by the use of hyperthermic sensitizers. The potential benefits of chemotherapeutic agents plus localized hyperthermia remain largely unexplored.

In summary, clinical studies have established that localized hyperthermia can significantly enhance irradiation cytotoxicity in superficial human tumors, typically with less enhancement in normal tissues. The optimization of such treatments by the careful evaluation of the above and other factors in human trials can allow the more effective integration of hyperthermia into standard clinical practice.

References

9. Bicher, H. I., Sandhur, T. S., and Hetzel, F. W. Hyperthermia and radiation in

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Table 6

<table>
<thead>
<tr>
<th>Institution</th>
<th>Ref.</th>
<th>No. of treatment courses</th>
<th>Toxicity</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>Duke University</td>
<td>U et al. (43)</td>
<td>53</td>
<td>Superficial burn</td>
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<td>M. D. Anderson</td>
<td>Corry et al. (11)</td>
<td>30</td>
<td>Deep burn</td>
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<td>Roswell Park</td>
<td>Scott et al.*</td>
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<td>Pain</td>
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<td>Stanford University</td>
<td>Marmor et al. (30)</td>
<td>52</td>
<td>Radicular pain</td>
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<td>Washington University</td>
<td>Perez et al. (40)</td>
<td>101</td>
<td>Blistering</td>
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<td>Pain</td>
<td>23</td>
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<td>Ulceration</td>
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Localized Hyperthermia


The Clinical Efficacy of Localized Hyperthermia

John L. Meyer

Cancer Res 1984;44:4745s-4751s.