Problem of Sequence and Fractionation in the Clinical Application of Combined Heat and Radiation

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Abstract

Tumor control, thermal enhancement, and therapeutic effect have been evaluated in a series of studies on 77 patients with a total of 163 superficial lesions by using different protocols of combined radiotherapy and local external hyperthermia. Local tumor control and recurrence rate were constantly better in lesions treated with combined treatment in comparison with those treated with radiotherapy alone, regardless of treatment schedule. The enhancement of tumor control appeared to be related to both the magnitude of the applied heat and the size of radiation fractions, in that an increase in either produced an increase in tumor control. When tumor and critical normal tissue were heated to the same temperature, the immediate combination of heat and large radiation fractions resulted in a pronounced enhancement of tumor control, but the concomitantly heated normal tissue showed an increased percentage of radiation reaction, resulting in a low therapeutic advantage. By introducing an interval of 4 hr between the two modalities or by delivering fewer heat fractions during the course of a conventional fractionation radiotherapy, the enhancement of tumor control was lower, but the increase in skin reaction was minimal, resulting in a clearly improved therapeutic effect. When the tumor could be preferentially heated with respect to normal tissue, the immediate combination of the highest hyperthermic treatment and the largest radiation fractions resulted in the best therapeutic advantage, since no increase of skin reaction was observed.

Introduction

The combination of hyperthermia and radiation is a treatment modality which has been widely studied in recent years with abundant experimental and early clinical evidence of the potential benefit of such treatment in cancer therapy (1, 3–6, 11, 12, 16, 17, 19, 25). The rationale for such combination is based partly on a hyperthermic radiosensitization and partly on a direct hyperthermic cytotoxicity against acidic, nutritionally deprived and chronically hypoxic, radioresistant tumor cells (6, 11, 20, 25). However, the interaction between heat and radiation is complex and not yet completely understood.

Most experimental studies are related to a single application of heat and radiation, but, in the clinical situation, a fractionated treatment schedule is most likely (1, 4, 17–19). The relevance of some treatment parameters, such as the time-temperature relationship, the sequence of the 2 modalities, the fractionation interval, and the size of radiation fractions in determining the response of tumors and normal tissues to fractionated combined treatment, depends mainly on the influence of some physiological and partly unknown factors, such as the amount of blood flow, the degree of pH, the time scale for repair of the hyperthermic radiosensitization, and, especially, on the kinetics and magnitude of the phenomenon known as thermotolerance (i.e., a temporary heat resistance induced by a prior heat treatment) (10, 20, 22). Furthermore, a fractionated hyperthermic treatment may induce in tumors and in normal tissues a modification of the blood flow and of the environment such that the response to subsequent treatment may be changed. In this situation, a certain degree of confusion and uncertainty may derive in the design of clinical scheduling, making it difficult to know whether the addition of heat to radiation may result in a therapeutic advantage with respect to radiation alone.

In this paper, we present a series of studies which have been carried out at our institute by testing, in patients, several combination schedules with the aim of making clinical observations, similar to those which are generally obtained in animals by using fractionated hyperthermia and radiation (17, 19, 24), and of discussing the optimal approach to cancer therapy by critically considering the influence of the various biological phenomena.

Materials and Methods

The studies reported here are based on the treatment of 77 patients with 2 or more superficial lesions for a total of 163 lesions (Table 1). This allowed us to compare, in the same patients, the response of both radiotherapy alone and combined treatment. Many of these tumors failed to respond to conventional treatments, including radiotherapy, and most of the patients had very advanced lesions and/or disseminated disease.

The treatment techniques have been extensively described in previous papers (1, 2, 4). Briefly, radiation was given with electrons of various energies or with 6-MeV photons by means of linear accelerators up to total doses which varied according to the several treatment protocols reported below. Heat was delivered by means of a conventional 27-MHz diathermia or by microwave generators, which were operated at frequencies of 400 to 500 MHz or of 2450 MHz, using contact or noncontact applicators of appropriate length and size. Temperature was monitored at the regular intervals, with the power off, by inserting an 18-gauge constantan-copper thermocouple wire inside the plastic lumen of a standard intracatheter probe placed previously at the base of the lesion. More recently, we have used microthermocouples of 100-μm diameter (Medtronic, Minneapolis, MN) or multisensor probes (IT17 thermocouples) (Bailey, Saddle Broo, NY) which react poorly with the electromagnetic field, allowing us to continuously monitor the temperature in different tumor locations.

The time-temperature relationship varied according to the treatment protocols used in this study, which are summarized in Table 2. In the first protocol, radiation was delivered as 3 fractions/day of 1.5 to 2 Gy each, at 4-hr intervals, up to a total dose of 60 Gy; heat, at 42.5°C for 45 min, was applied every other day, immediately after the second daily fraction of radiation, for a total of 7 hyperthermic sessions.

In the second protocol, radiation was given as conventional fractionation (i.e., one daily fraction of 2 Gy) up to a total of 50 Gy; heat, at...
43.5° for 45 min, was applied once or twice a week immediately after the last or the second and the last radiation fractions of each week, for a total of 5 or 10 hyperthermic sessions.

In the third protocol, radiation was given as 2 weekly fractions of 5 Gy up to a total of 40 Gy; heat, at 42.5° for 45 min, was applied either immediately (immediate treatment) or 4 hr after (delayed treatment) each radiation fraction, for a total of 8 hyperthermic sessions.

Finally, in the fourth protocol, radiation was delivered as 2 weekly fractions of 6 Gy up to a total dose of 30 Gy, and heat, at 45° for 30 min, was applied immediately after each radiation fraction for a total of 5 hyperthermic sessions; in this case, the skin around the lesion was cooled by means of circulating cold water.

Heating time was the effective time at the treatment temperature. The procedures were explained to the patients and family members, and the option of alternative therapies was fully discussed.

Tumor response was simply recorded as failure or success (i.e., total disappearance of lesion) at the end of treatment or soon after. Recurrences were recorded during a follow-up period ranging from 6 to 18 months. The peak acute skin reaction (moist desquamation) was simply recorded as absent or present.

Statistical significance has been attempted by means of the χ² test, although, in this instance, every difference should be considered significant as the response to different schedules concerns the same tumor in the same patient, the only possible variant being the size of lesion.

Results

The results are shown in Table 3. Tumor response to combined treatment was constantly better with respect to radiation alone for whichever treatment schedule was used. The difference was statistically significant in lesions treated with Protocols 1, 2b, and 4. The highest improvement was obtained with the protocol which utilized large radiation fractions and intense heating; 87% (13 of 15) and 33% (5 of 15) complete tumor responses were obtained after combined modality and radiation alone, respectively.

By using large radiation fractions, the immediate addition of

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<td>Histology</td>
<td>Site</td>
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<td>Squamous cell carcinoma</td>
<td>Head and neck, lymph nodes</td>
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<td></td>
<td>Vulva, skin, lymph nodes</td>
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<td>Lung supraventricular lymph nodes</td>
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<td>Adenocarcinoma</td>
<td>Breast, skin recurrences</td>
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<td></td>
<td>Lung, skin, lymph node metastases</td>
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<td>Rectum, skin metastases</td>
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<td>Stomach, skin metastases</td>
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<td>Kidney, skin metastases</td>
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<tr>
<td>Melanoma</td>
<td>Recurrences of skin and nodes</td>
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<td>Undifferentiated cell carcinoma</td>
<td>Lung, skin, scalp metastases</td>
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<td>Unknown, skin metastases</td>
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<td>1. Immediate/delayed heat vs. radiation alone</td>
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<td>Immediate heat vs. radiation alone</td>
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<td>3. Immediate heat vs. radiation alone</td>
<td>42.5°</td>
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<td>Delayed heat vs. radiation alone</td>
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<td>4. Immediate heat vs. radiation alone</td>
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<th>Table 3</th>
<th>Response to treatment</th>
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<td>Tumor response</td>
<td>Radiotherapy + heat therapy</td>
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<td>Treatment protocol</td>
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<tr>
<td>1. Immediate/delayed (moderate heat therapy)</td>
<td>19/26 (0.73)</td>
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<td>2. Immediate (5 heat therapy fractions) (moderate heat therapy)</td>
<td>9/14 (0.64)</td>
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<td>Immediate (10 heat therapy fractions) (moderate heat therapy)</td>
<td>7/9 (0.78)</td>
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<tr>
<td>3. Immediate (moderate heat therapy) Delayed (moderate heat therapy)</td>
<td>10/13 (0.77)</td>
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<td>4. Immediate (intense heat therapy)</td>
<td>13/15 (0.87)</td>
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* Numbers in parentheses, percentages.
* Statistical difference, p ≤ 0.05.
* Statistical difference, p = 0.01.
heat resulted also in an increase of the percentage of skin reaction. 64% (9 of 14) versus 36% (5 of 14) moist desquamation was observed after combined and single modality, respectively. However, when an interval of 4 hr was introduced between the 2 modalities or when the skin was cooled by means of circulating cold water, the percentage of skin reaction was less, approaching, in Protocol 4, that observed after radiation alone.

The failure pattern of the lesions treated with Protocol 1 (i.e., radiotherapy given as 3 small fractions per day combined, every other day, with moderate heat) is shown in Chart 1. The percentage of total failures after radiation alone increased from 58% at the end of treatment to 85% at 18 months, in contrast with the lesions treated by the combined modality in which, after a small initial increase, the percentage of total failures remained almost at a plateau level of about 35%. Therefore, the addition of heat seems to be not only more effective in achieving a higher response rate but also in maintaining tumor control during follow-up.

This is shown more clearly by the ratio of combined to single-modality failure which represents the actual thermal enhancement of tumor response, since different lesions were treated, in the same patients, with different modalities. In this trial, the ratio had an almost constant value of about 0.46 throughout the whole follow-up period, indicating that, during this period, in more than one-half of the patients, recurrences occurred only in the group of lesions treated with radiotherapy alone (Chart 5).

Chart 2 shows the failure pattern of the lesions treated with Protocol 2 (i.e., radiation given as daily fractions of 2 Gy combined with moderate heat once or twice a week). The percentage of total failure at the end of treatment and at 6 months ranged from 65 to 76% after radiotherapy alone. This range, in contrast, was 36 to 43% when 5 hyperthermic fractions, given once a week, were combined with radiotherapy. The combination of radiation with 10 hyperthermic fractions, given twice a week, achieved the lowest failure rate (22%), and no recurrence was seen during the follow-up.

The ratio of combined to single-modality failure, using 5 hyperthermic fractions, had an almost constant value of about 0.55 during the follow-up period indicating, as in the previous protocol, a higher effectiveness of the combined than of the single-treatment modality. The failure ratio at the end of treatment, when using 10 hyperthermic fractions, was lower (0.34) than that when using 5 hyperthermic fractions and decreased to 0.29 at 6 months, indicating that the schedule was more effective than the latter in controlling tumors.

Chart 3 shows the failure pattern of the lesions treated with Protocol 3 (i.e., radiotherapy given as large biweekly fractions combined with immediate or delayed moderate heat). The percentage of total failures at the end of treatment and at 6 months ranged from 23 to 31% and from 33 to 50% in the lesions treated with immediate and delayed heat, respectively. This range, in contrast, was 62 to 81% after radiotherapy alone.

The ratios of combined to single-modality failure ranged from 0.53 to 0.62 for the delayed and from 0.37 to 0.38 for the immediate treatment, indicating that the latter schedule was more effective than the former in controlling tumors. Finally, in the trial using Protocol 4 (i.e., radiotherapy given as large biweekly fractions combined with immediate intense heating), the failure rate ranged from 67% at the end of treatment to 87% at 6 months after radiotherapy alone. After combined modality, only 13% of the lesions failed, and none recurred during the follow-up period (Chart 4). In this case, the ratio of combined
Chart 4. Failure rates of the lesions treated with Protocol 4 (i.e., radiotherapy given as 2 large weekly fractions combined with intense heat applied immediately after each radiation fraction). ○, radiation plus heat therapies; •, radiotherapy alone. Reprinted from Ref. 4 with permission of Pergamon Press.

Chart 5. Ratio of combined to single-modality failure after different treatment protocols. □, small radiotherapy fractions combined with immediate and/or delayed 42.5° heat therapy; ▲, small radiotherapy fractions combined with immediate 5-fraction 43.5° heat therapy; ⊗, small radiotherapy fractions combined with immediate 10-fraction 43.5° heat therapy; △, large radiotherapy fractions combined with delayed 42.5° heat therapy; △, large radiotherapy fractions combined with immediate 42.5° heat therapy; ○, large radiotherapy fractions combined with immediate 45° heat therapy. RT, radiotherapy; HT, heat therapy.

The enhancement of tumor control by the addition of heat does not always mean an increase in the therapeutic effect. Chart 7 shows the skin and tumor TER as a function of the number of heat fractions. With the schedules using small radiation fractions, the tumor TER increased by increasing the number of heat fractions; the skin TER, in contrast, tended to be almost constant, with little variations between 1.1 and 1.26. Consequently, also, the therapeutic gain (i.e., tumor to skin TER) increased by increasing the number of heat fractions (Chart 8).

The TER values obtained with the schedules using large radiation fractions are reported separately (Chart 7). Also here, the TERs of tumors were higher than those of skin. However,
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Water. Consequently, the highest therapeutic gains (2.08) were obtained with this schedule (Chart 8).

In Chart 9, the tumor and skin TERs are plotted as a function of the number of radiation fractions. The tumor TER decreased by increasing the number of radiation fractions. However, the TER in the skin decreased, initially, more than that in the tumor. Consequently, the therapeutic gain appeared to increase initially by increasing the number of radiation fractions, reaching a plateau after 25 fractions (Chart 10).

The TER values obtained with the schedules using both intense heating and delayed moderate treatment are reported separately. With the use of the latter schedule, the enhancement in the tumor was lower than that observed after the immediate treatment; however, the enhancement in the skin was less (Chart 9). Consequently, the therapeutic gain after 8 radiation fractions was higher with the delayed than it was with the immediate

the enhancement in the skin was higher with the immediate than it was with the delayed schedule. Consequently, the therapeutic gain was higher with the latter than it was with the former schedule (Chart 8). The data points for the schedule using the largest radiation fractions combined with the widest magnitude of hyperthermic treatment (i.e., 5 fractions of 45° for 30 min, or 1350 min equivalent time at 42.5°), also reported separately, show that the highest tumor TER and the lowest skin TER were accomplished with this schedule. However, in this case, the skin surrounding the lesions was actively cooled by circulating cold

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treatment (Chart 10). By using intense heating, the enhancement in the tumor was the highest and, because of the skin cooling used here, the enhancement in the skin was the lowest (Chart 9). Consequently, the highest therapeutic gain was accomplished with this treatment schedule (Chart 10).

Discussion

Our clinical findings indicate that the highest tumor TER was obtained when the largest radiation fractions were immediately combined with the widest magnitude of hyperthermic treatment, utilizing the mechanism of hyperthermic radiosensitization. However, an enhanced tumor TER does not mean an increased therapeutic effect, since the skin TER can also be increased. In fact, when tumor and critical normal tissue were heated to the same temperature, the immediate combination of heat and large radiation fractions resulted in a pronounced enhancement of tumor control, but the concomitantly heated normal tissue also showed an increased percentage of radiation reaction, resulting in a low therapeutic advantage. In this situation, a differential effect could be obtained, utilizing the mechanism of the selective hyperthermic cytotoxicity against the acidic and chronically hypoxic tumor cells (6, 11, 15, 18, 19), by introducing an interval of 4 hr between the 2 modalities (delayed treatment) or by delivering few heat fractions during the course of a conventional fractionation radiotherapy (i.e., numerous, small radiation fractions). With these schedules, the enhancement of tumor control was lower than with the previous schedule, but the increase of skin reaction was minimal, resulting in a clearly improved therapeutic effect.

When the tumor could be preferentially heated with respect to normal tissue, the immediate combination of the highest hyperthermic treatment and the largest radiation fractions, utilizing the mechanism of the hyperthermic radiosensitization, resulted in the best therapeutic advantage, since no increase of skin reaction was observed. However, with the current heating techniques, it is difficult to achieve a preferential tumor heating, although heat treatment itself may cause a collapse of the tumor microvascularization while increasing the perfusion of the surrounding normal tissue (8, 23).

Our data indicate also a decrease of TERs by increasing the number of radiation fractions. This could be due to both the lower number of radiation fractions sensitized by heat and/or less hyperthermic impairment of sublethal damage repair at small radiation fractions, since cell killing, at low doses, predominantly occurs by "single heat" lethal events. However, skin TER decreased more than did tumor TER, probably due again to the mechanism of the selective hyperthermic cytotoxicity against the acidic, and chronically hypoxic, tumor cells (6, 11, 15, 18, 19). Consequently, the therapeutic effect increased by increasing the number of radiation fractions and reached a plateau after 25 fractions.

As mentioned, thermotolerance is one of the most relevant factors which influences the response to a fractionated combined treatment. Thermotolerance probably occurs in all normal tissue and tumors (10) and has also been found to influence the effect of the combined heat and radiation (14, 22). To achieve an optimal therapeutic effect, thermotolerance should be avoided in the tumor and, possibly, maintained in the normal tissues. Unfortunately, considerable variation in the kinetics and magnitude has been found in different tissues (10, 14, 22), and it is not possible, at present, to know the development and the time course of thermotolerance in a given tumor or normal tissue. However, there is a known relationship between the magnitude and the kinetics of thermotolerance and the amount of heat damage induced by the priming hyperthermic treatment, in that thermotolerance will appear later and will be higher as the priming heat fraction is larger (13, 14, 22). In the clinical settings, because of the less than optimal thermometry systems used and the inhomogeneity of the thermal distribution achieved with the use of the presently available equipment, several portions of the tumor are heated to different temperatures. In this situation, thermotolerance will develop with different kinetic patterns in the different parts of the tumor which receive different heat damage (22). The consequence of this is that, in the differently heated tumor area, thermotolerance will be expressed to a different extent at the time of the subsequent fraction (22). These problems are probably some of the reasons why the clinical responses to different regimens of fractionated hyperthermic treatments appear to be similar, despite different time-temperature relationships and fractionation intervals used in several clinical studies (19).

It is beyond the purpose of this paper to discuss in detail the heating techniques used in this study. They have been partly described already (1, 2, 4) and partly will be reported in the future. Since the lesions treated in this study were superficial and relatively small, they can probably be assumed to have been treated with an adequate and relatively homogeneous heating, although in many cases the temperature was not monitored continuously and only by means of a single probe inserted at the base of the lesions. Our data show that increasing the number of hyperthermic treatments causes an increase of the tumor TER without a substantial increase of the skin TER, probably again, of the selective hyperthermic cytotoxicity against the acidic and chronically hypoxic tumor cells. Consequently, the therapeutic effect increased by increasing the number of hyperthermic treatments. Although the number of radiation fractions associated with hyperthermia is different in the several schedules used in our study and so are the interval and magnitude of the heat treatments, our data show that, with the same number of radiation fractions, tumor TER increases by doubling the number of equal hyperthermic treatments from 5 to 10. This suggests that 10 biweekly heat fractions do not induce thermotolerance in human tumors, although the problem can only be clarified with more clinical data.

Further technological advances are urged to clinically confirm the biological predictions of the tumor and normal tissue responses and to optimize the combination of heat and radiation in the treatment of patients with malignant disease.

References


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