Review

Efficacy of Mild Temperature Hyperthermia in Combined Treatments for Cancer Therapy

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Abstract: Most patients treated with hyperthermia have tumors which are refractory advanced and/or recurrent tumors which cannot be controlled by conventional treatments, and their performance status is often poor. Thus, it is very difficult for these patients to maintain a physical position suitable for heating tumors whose temperatures can be maintained at more than 42°C for nearly an hour (in order to induce direct toxicity in tumor cells). Furthermore, we sometimes cannot help interrupting the heating due to acute adverse reactions such as severe pain. In addition, it is also very difficult to heat tumors homogeneously to temperatures over 42°C, using currently available heating devices. In many clinical studies in which hyperthermia was used to enhance the efficacy of radiotherapy, tumor temperatures could be increased only to the 40-41.5°C range. Under these conditions, heat-induced cell death, increased cellular radiosensitivity, and vascular damage are likely to be insignificant in spite of the increased response of tumors to radiotherapy. Recently, mild temperature hyperthermia (MTH)-induced physiological effects on tumors have been shown to lead to an increased blood flow and a resulting increase in tumor oxygenation, and this could lead to increased radiosensitivity if radiotherapy was used after MTH, and to an increase in chemosensitivity *via* an increased transport of drugs into tumors. Therefore, if the clinician's goal is to keep the tumor temperature in the 40-41°C range, it is possible to reduce a patient's burden, make it easier to maintain a patient in a suitable position for heating, and avoid interrupting the heating session. In thermoradiotherapy, when heating at temperatures higher than 42-43°C can be warranted, hyperthermia should be performed after radiotherapy. However, when heating over 42°C is difficult, an alternative useful approach may be to reverse the order of radiotherapy

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and hyperthermia : specifically apply radiotherapy subsequent to tumor oxygenation-inducing MTH.

Key Words : mild temperature hyperthermia, thermoradiotherapy, sequence of heating and radiation, thermochemotherapy, quiescent cells

Introduction and Background

In the mid-to-late 70s, leading scientists placed great emphasis on the quantitative evaluation of the cytotoxic effects of elevated temperatures[1]. In mid-1980s, the first concepts for a thermal dose were suggested, and it was also shown that significant cell killing could occur if cells or tissues were heated to over 42°C for 1 hour or more[2]. Thus, clinical thermal treatment goals and equipment performance design criteria focused primarily on achieving cytotoxic temperatures.

Studies of the biological basis for cytotoxic high temperature hyperthermia then followed[3]. First, it was possible to kill cells with heat, particularly when temperatures were over 42°C for 1 hour or more. Secondly, heat could also kill cells which were particularly resistant to radiation, such as cells in the late S-phase of the cell cycle and hypoxic cells. Thirdly, heat induced significant thermo-radiosensitization and chemosensitization, partly by inhibiting DNA damage repair. Fourthly, the vasculature of tumors appeared to be more thermally sensitive than normal vasculature, suggesting that tumor tissue would be more thermally sensitive than normal tissues. All of these findings were of interest, however, there were great difficulties in generating adequate heat to kill cells directly[4]. The conclusions from clinical cytotoxic hyperthermia observed over the last two decades are described below.

1. Hyperhermia prescriptions define goals such as reaching temperatures of over 42℃ for 1 hour or more per session

A primary rationale for the use of hyperthermia in combination with radiotherapy has been that hyperthermia is equally cytotoxic toward fully oxygenated and hypoxic cells and that it directly sensitizes both fully oxygenated and hypoxic cells to radiation[3]. Such cytotoxicity and such a radiosensitizing effect would be expected to be significant when the tumor temperature is elevated at least to over 42°C for 30-60 min. Unfortunately, in clinical practice, the generation of sufficient heat to raise the temperature of human tumors to this level was rarely achieved with currently available heating devices[4].

2. Heat treatment should be given only twice per week

This rationale came from fears that too frequent applications of heat could lead to the induction of thermotolerance[5]. Repair of DNA damage can occur at temperatures as low as 40°C, but at that temperature, thermotolerance will not be induced during or after heating[6].

3. Vascular damage in tumors leads to transient hypoxia so hyperthermia treatment should not be given before radiotherapy treatment

It is now suggested that mild temperature hyperthermia (MTH) actually causes tumor reoxygenation[7]. In contrast, higher temperature heating leads to vascular damage and hypoxia[8]. Under these conditions, it may be better to apply MTH before radiation in order to take advantage of

reoxygenation effects on the day of heating as well as the day after heating.

4. Equipment design criteria

The difficulty of achieving therapeutically effective temperatures, combined with the technical difficulties of applying hyperthermia, and the lack of an adequate commercial return led to the loss of commercial interest in hyperthermia technology at some of the larger equipment manufacturers like Varian[9]. In addition, at least 1 hour is required for one heating session, and this time-consuming task is another big economic problem for clinics. Thus, until now, there has not been a large amount of clinical data available on the efficacy of hyperthermia.

In many clinical studies over the past two decades on the efficacy of hyperthermia for various human tumors, tumor temperatures could seldom be raised to cytotoxic levels, that is to temperatures over 42-43°C[4]. In fact, in many past clinical studies in which hyperthermia was found to enhance the efficacy of radiotherapy, the tumor temperatures could be raised only to the 40 to 41.5°C range. The cumulative minutes of treatment in which 90% of the measured intratumor temperatures (T90) exceeded 39.5°C was strongly associated with complete responses in superficial tumors[4,10]. The cumulative time in which 50% of the intratumor temperatures (T50) exceeded 41.5°C was strongly associated with the presence of $>$ 80% necrosis in soft tissue sarcomas resected after radiotherapy and hyperthermia[4,10].

Usefulness of mild temperature hyperthermia (MTH) in cancer therapy

1. Combination with radiation

The following hypothesis has been suggested[10]: prognostically important thermal doses are based on the lowest temperatures achieved within tumors, and these thermal doses are well below those used in most laboratory studies which have provided the traditional rationale for hyperthermia. Direct thermal cytotoxicity and thermal radiosensitization are insignificant at these low thermal doses, thus, it has been hypothesized that hyperthermia at low thermal doses can be effective because it causes reoxygenation and hence radiosensitization *in vivo*. Actually, MTH, that is, heating to 39-41.5°C range, causes a long lasting increase in tumor oxygenation through an increase in blood flow. In contrast, heating at temperatures high enough to reduce tumor blood flow decreases tumor oxygenation[7,11].

It has also been reported that MTH improves tumor oxygenation in canine tumors[11–14]. In contrast, a median temperature of over 44°C resulted in a decrease in tumor oxygenation 24 hours after heating[11]. MTH-induced changes in oxygenation in human breast tumors have also been investigated[11]. The tumors were treated with fractionated radiotherapy, and MTH was initiated during the first week of radiotherapy. The tumor *p*O2 increased up to fivefold at 24 hours after the first hyperthermia treatment[11]. Thus, it is thought that the increase in tumor *p*O2 observed during and soon after MTH resulted from an increase in oxygen supply through an increase in blood flow, and the later increase in tumor *p*O2, that is at 24 hours after heating, is caused by both increased blood flow and decreased oxygen consumption due to thermoradiotherapy-induced tumor cell death or tumor cell damage[7,11] (Fig. 1). Furthermore, MTH at 41.5°C for 60 min prior to tumor irradiation was significantly effective in enhancing radiation-induced cell killing[11]. An important finding in these studies is that heating at relatively mild temperatures was superior to heating at high tempereatures in causing reoxygenation to

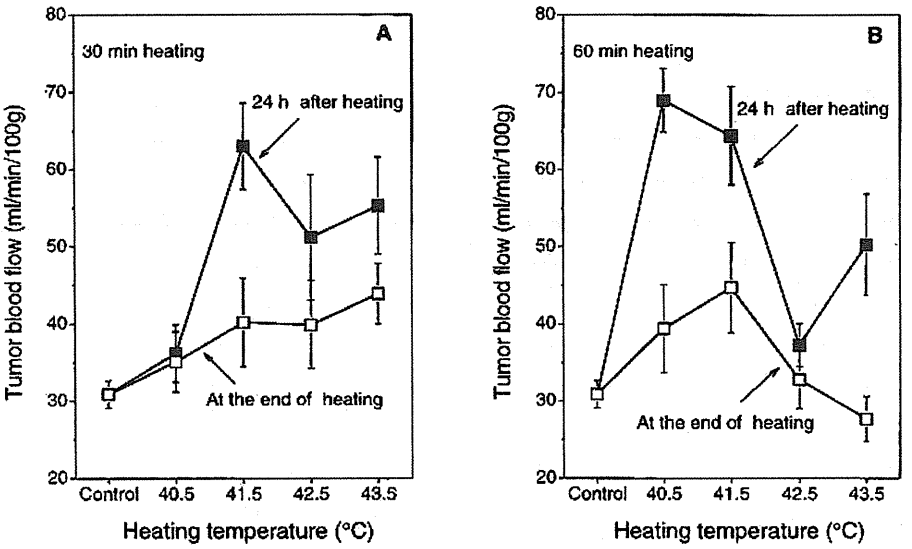

Fig. 1. Median tumor $pO2$ values in control and treated R3230 Ac tumors measured within 12-15 min or at 24 hours after heating at various temperatures for 30 min (panel A) and 60 min (panel B). Each point represents the mean±standard error of 10-26 tumors (Song C.W. et al.[11]).

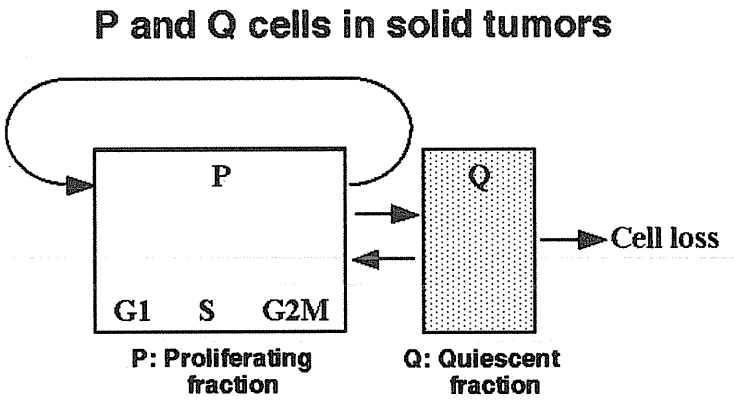

Fig. 2. The concept of proliferating (P) and quiescent (Q) cells in solid tumors. Q cells are non-dividing viable cells in solid tumors.

occur in tumors and in inducing a more complete response to radiotherapy.

In a previous study on the effects of MTH on the size of the hypoxic fraction in murine solid tumors, the following was observed. In general, the quiescent (Q) tumor cell population, which is the non-dividing viable fraction of the tumor cell population (Fig. 2) contained a greater hypoxic fraction than the total (the proliferating cell fraction P+Q) tumor cell population[12]. As a result, the Q tumor cell fraction is more resistant to radiation therapy than the proliferating, or P, fraction of the tumor cell population. MTH decreased the size of the hypoxic fraction in quiescent or Q cells more markedly than in the total cell population, regardless of the p53 status of the tumor cells[13]. The minimum values for the hypoxic fractions in both, the total population and the quiescent or Q cell fraction, were reached at 6 hours after mild heating. Therefore, MTH could conceivably result in radio-sensitization because of its potential to oxygenate the hypoxic fractions of heated tumors (Fig. 3). The time course of changes

in the decrease in the hypoxic fractions of the total and Q cell populations after MTH suggested that irradiation within 12 hours after mild heating may be a potentially promising therapeutic method for controlling the radio-resistant Q fraction of the tumor cells, especially when it is difficult to elevate the tumor temperature sufficiently to cause vascular damage, kill tumor cells, and directly radio-sensitize the tumor cells within solid tumors[14].

MTH at 40 to 41°C, if employed alone, is supposed to produce almost no cytotoxic effects[15]. Based on a formula used extensively for measuring thermal doses, CEM43°C T90 (the number of cumulative equivalent minutes at 43°C exceeded by 90% of the monitored points within the heated tumor), the thermal dose value is less than 1.0[2]. Under this criteria, almost no toxicity or cytotoxic effects would be caused by the use of MTH[16]. However, both *in vitro* and *in vivo*, when combined simultaneously with low dose-rate irradiation, MTH has been reported to efficiently inhibit cell recovery which could occur with the use of a decreased or lower dose rate[17]. Meanwhile, heating at 41°C simultaneously with irradiation at a dose rate of 4-20 Gy/hr and below 1 Gy/hr is thought to eliminate the dose-rate-sparing effect by blocking split-dose repair (sublethal repair) and cell proliferation, respectively[17].

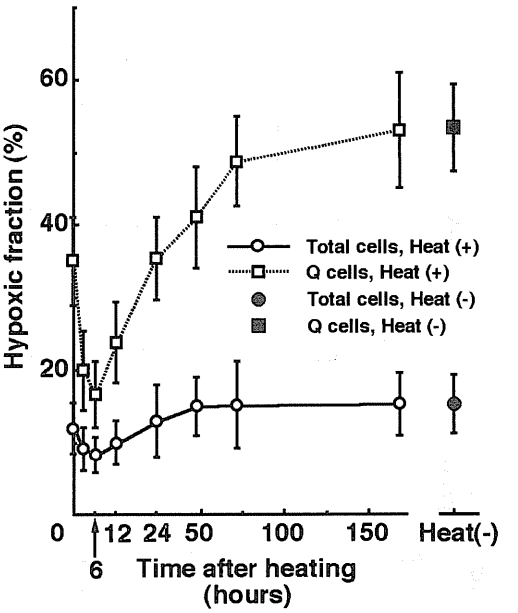

Fig. 3. Changes in the hypoxic fractions of total (open circles) and quiescent (open squares) tumor cell populations after mild temperature hyperthermia (40°C, 60 min). The hypoxic fractions of the total (solid circle) and quiescent (solid square) tumor cell populations for tumors which were not heated are also shown. Bars represent 95% confidence limits[14].

2. Combination with other treatments

If thermochemotherapy is used with mild temperatures, the effects of melphalan, cyclophosphamide, ifosphamide and cisplatin were found to be markedly enhanced by mild heating when compared to treatment at room temperatures *in vivo*[18]. Furthermore, based on data from in-vitro studies, the activation energies obtained from Arrhenius plots for cisplatin, bleomycin and 5-fluorouracil used with MTH below 41.0°C were significantly smaller than the energies seen with thermal applications using temperatures above 41.0°C. This means that thermal enhancement of the cytotoxicity of many chemotherapeutic agents increases most significantly at temperatures below 41.0°C[18]. This implies, that in general, thermal enhancement in chemotherapy is could be feasible in combination with MTH.

According to previous reports, MTH sensitized tumor cells to the hypoxia-specific cytotoxin tirapazamine, and induced cytotoxicity more markedly in p53-mutated tumor cells and intratumor Q cell populations than in wild type p53 tumor cells and in the total tumor cell populations, respectively[19] (Fig. 4). This finding suggests that MTH could provide a useful tool in controlling cancer therapy-resistant p53-mutated tumors and intratumor Q cell populations. When MTH was combined with chemoradiation therapy, MTH significantly increased the sensitivity of the total cell population

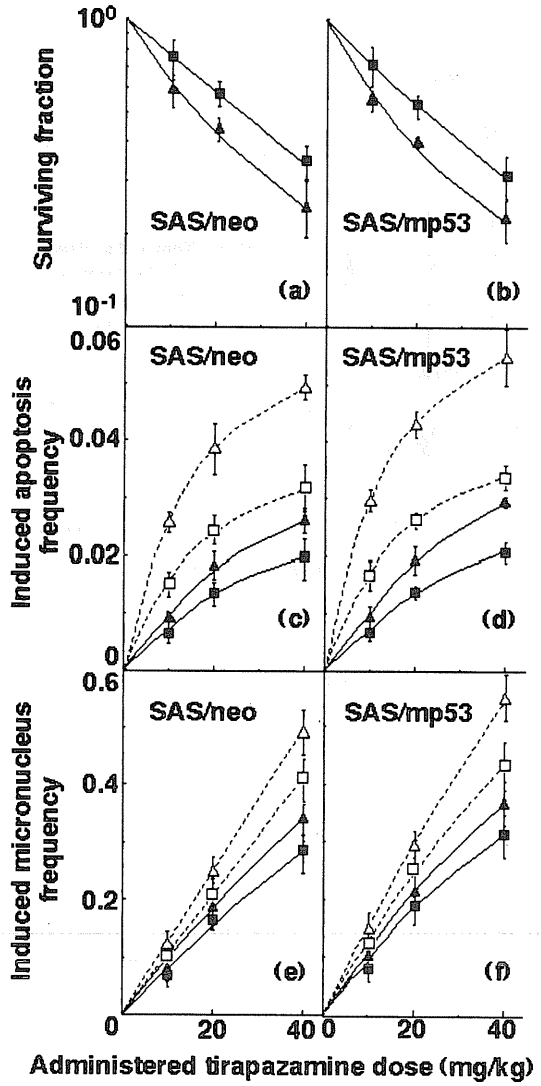

Fig. 4. Cell-survival curves for SAS/neo (a) and SAS/mp53 (b) cells, tirapazamine dose-response curves for induced apoptosis frequency in SAS/neo (c) and SAS/mp53 cells (d), and tirapazamine dose-response curves for induced micronucleus frequency in SAS/neo (e) and SAS/mp53 cells (f) as a function of an intraperitoneally administered dose of tirapazamine (10, 20 and 40 mg/kg). In both SAS/neo and SAS/mp53 tumors, combined treatment with mild temperature hyperthermia (MTH, 40°C, 60 min, triangles) caused a decrease in the surviving fractions when compared with tirapazamine alone (squares). In both total (solid symbols) and quiescent (open symbols) cells, combined treatment with MTH (triangles) increased induced apoptosis and micronucleus frequencies when compared with tirapazamine alone (squares). Bars represent 95% confidence limits[19].

when combined with cyclophosphamide, bleomycin, cisplatin or tirapazamine, and the sensitivity of the Q cells when combined with bleomycin or tirapazamine[20] (Fig. 5). Moreover, even after treatment with the anti-angiogenic agent TNP-470, combined treatments with tirapazamine and MTH, whether or not other cytotoxic treatments such as γ-ray irradiation or chemotherapy using cisplatin were used, was useful for sensitizing tumor cells *in vivo* including Q cells[21]. With boron neutron capture therapy (BNCT), which has been performed at Kyoto University (Kyoto University Reactor), ^{10}B atoms from administered ^{10}B-carriers have to be distributed into tumor tissues as selectively and homogeneously, and to as high a concentration as possible before exposure to low-energy thermal or epithermal neutron beams from the reactor. Under these conditions, the use of MTH was shown to enhance the delivery of ^{10}B into tumor cells, especially into the Q tumor cell population[22] whose ^{10}B uptake potential is thought to be much lower than the P tumor cell population[23]. This resulted in the survival of more Q cells than P cells after BNCT therapy.

The immune response to tumors is also of interest. For example, the cytotoxic activity of NK cells was drastically attenuated by high temperature cytotoxic hyperthermia. However, it has been suggested that MTH may activate both the innate and adaptive immune systems through the activation of NK cells and through a decrease in the number of regulatory T cells[24].

Research into inducing an increase in the expression of therapeutic genes within cells with MTH using hsp promoters is also underway. A report has shown that MTH is more effective in promoting heat-mediated suicide-gene expression than high-temperature therapy[25].

3. The viewpoint from the actual clinical scene

Most patients who received hyperthermia

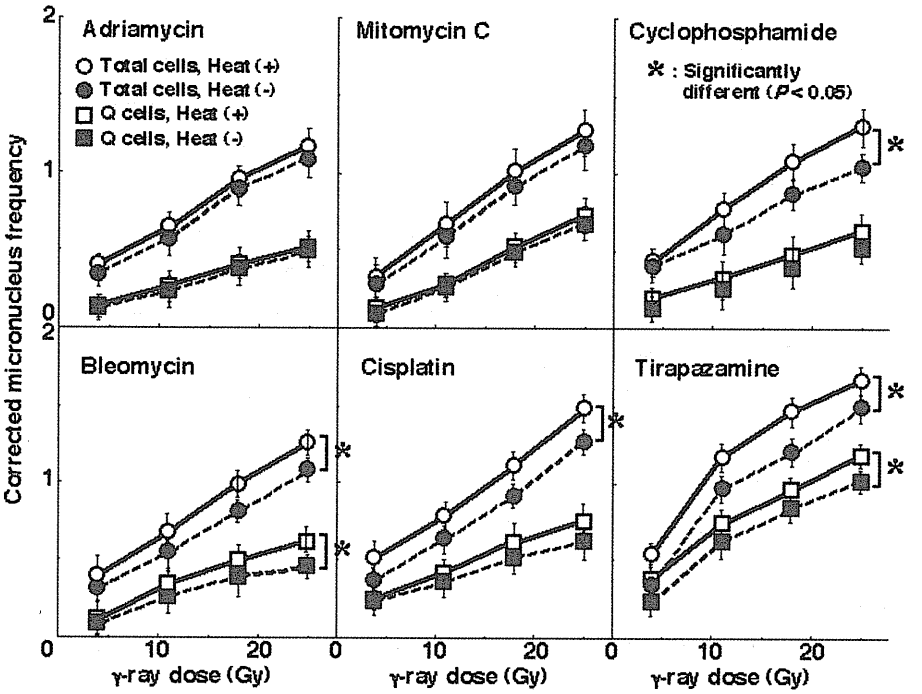

Fig. 5. γ-Ray dose-response curves for corrected micronucleus (MN) frequency (MN frequency - C, where C is the MN frequency in cells from tumors in animals not given γ-rays) in the total cell popuation and in quiescent (Q) cells from tumors in mice given adriamycin, mitomycin C, cyclophosphamide, bleomycin, cisplatin, or tirapazamine. Total cell population : ○ Mild heating (−) ; ● Mild heating (+). Q cells : □ Mild heating (−) ; ■ Mild heating (+). Bars represent 95% confidence limits[20].

treatments had large tumors that could not be controlled by other treatments, or were very refractory recurrent tumors which followed an initial anticancer treatment. Moreover, in many cases, patient performance status was not good. It is very difficult to keep patients a suitable position for heating tumors whose temperature should be kept at more than 42°C for approximately 1 hour. As a result, in some cases, hyperthermia cannot avoid being interrupted by an acute toxicity such as pain. It is very difficult to heat tumors homogeneously to over 42°C, using currently available heating devices. Therefore, by using a temperature under 41°C, it is possible to ease the burden on the patient, and it is more practical to maintain a patient in a position suitable for heating, and to avoid interrupting the application of heat.

In order to continue with the development of hyperthermic treatments, the physical, biological, and medical fields have to progress in step with each other. However, since there is little current progress in developing physics based devices, an easy-to-operate heating device is not available. In practice, with ideas from clinical practitioners who operate conventional heating devices, most heating sessions currently manage to be effective and to maintain an effective relationship between the heated sites and the heating devices with suitable arrangements made to optimize heating. Under these circumstances, the actual experiences of the current individual practitioners of hyperthermic medicine can be one of the most important factors influencing the outcome of tumor responses to hyperthermic treatment. This is why

it is not easy to standardize hyperthermic treatment as has been done for radiotherapy. When it is possible to heat tumors over 42°C in expectation of direct cytotoxicity to tumor cells during the first heating session, trying to heat tumors to over 42°C will be attempted at subsequent heating sessions. However, when it is impossible to heat tumors to over 42°C during the first heating session, changing to MTH becomes a reasonable protocol in succeeding sessions, and completing the entire course of heating treatment while avoiding an interruption of the heating process has to become at least one of the most important goals[14]. In fact, according to the author's clinical experiences with real world hyperthermic treatments, MTH combined with chemotherapy was found to be very useful for patients with low performance status who had post-radiotherapy recurrent refractory tumors, and it appears to be possible to suppress the growth of tumors and to keep the size of the tumors almost constant, even if it is impossible to decrease the size of the tumors[26]. Recently, some reports have also proposed and emphasized the significance of hyperthermia combined with chemotherapy as a tumor dormancy therapy in the treatment of refractory advanced and recurrent solid tumors[27,28].

Summary and Conclusions

Originally, hyperthermia was a heat treatment aimed at directly targeting tumor cells or the environment surrounding tumor cells[3,8]. In classical hyperthermic oncology, significant tumor cell killing is supposed to occur if cells or tissues are heated to over 42°C for 1 hour or more[2,3]. Radiosensitization and chemosensitization induced by heat treatment were thought to be able to play a significant role by partially inhibiting DNA damage repair[3]. However, clinical experience over the past 25 years has shown that it is not possible to routinely achieve thermal dose goals of over 42°C for 1 hour or more. It is now known that cytotoxic temperatures are only achieved in a small fractions of the tumor during typical hyperthermic treatments with currently available heating technologies (except with thermal ablation)[4].

The effects of MTH (39 through 41.5°C for 1 to 2 hours) on tissues are subtle, and have been largely ignored until recently. However, the subtle effects of MTH, including heat-mediated tumor reoxygenation[7] and the inhibition of sublethal and potentially lethal damage repair[17], provide a very strong rationale for using MTH in combination with radiotherapy. In addition, the physiological and cellular effects of MTH can improve the delivery of drug vehicles[29], activate promoters for heat-mediated gene therapy[25,30], and increase the immune response to tumors through a variety of mechanisms[23,31].

Therefore, in clinical thermoradiotherapy, when heating at temperatures higher than 42-43°C for 1 hour or more can be warranted, hyperthermia should be carried out right after radiotherapy. However, when heating over 42°C is difficult, another useful approach may be to reverse the order of radiotherapy and hyperthermia, namely, use radiotherapy following tumor oxygenation-inducing MTH[14]. When tumors are being heated, cancer patients can endure MTH very well because of few acute toxicities, and MTH is a useful and practical heating mode because even a relatively inexperienced clinical doctor can easily apply this therapy. Consequently, thermochemotherapy employing MTH also should be considered worthy of randomized clinical trials, similar to some on-going phase-I[32–34] clinical trials for the treatment of malignant tumors, although the only phase II clinical trial[35] had stopped because of enhanced drug-induced hepatotoxicity and the lack of objective responses of treated tumors in seventeen

eligible patients.

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Abstract in Japanese

癌治療における併用療法としての低温度温熱処置の有用性について

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要　　旨：従来，臨床における温熱併用放射線療法は，実験腫瘍に対する放射線照射と同時あるいは照射後の連続的加温処置のデータに基づき，放射線照射の直後に加温する様式がとられてきた．温熱治療を受ける患者の多くは，通常治療法では難治性で進行した腫瘍を有していたり，すでに癌治療を受けた後の再発症例である事も多く，いわゆる Performance status の良くない場合も多い．従って，温熱処置による直接的殺腫瘍効果を期待して，42°C以上の腫瘍内温度を確保しつつ 1 時間以上ある定まった体勢を保持させる事は至難の業であり，加温による疼痛などの有害事象によって治療中断に陥る可能性も非常に高い．さらに，現行の加温装置を用いて，加温対象となる腫瘍をほぼ均一に，直接的殺細胞効果を期待して 42°C以上に加温することは非常に困難である．他方，温熱療法の併用が放射線照射による治療効率を高めた事を示した従来の多くの報告においては，治療対象腫瘍の温度は 40-41.5°Cまでしか加温されていない．放射線治療による抗腫瘍効果の上昇を認めたにもかかわらず，加温による直接的な殺腫瘍細胞効果の上昇，放射線増感効果，及び腫瘍血管障害効果は，重要に思えない．最近，低温度温熱処置 (MTH) が誘導する血流増加作用やそれによる腫瘍酸素化作用などの生理的効果が，MTH 後の放射線照射による放射線増感作用や，薬剤の腫瘍分布上昇による化学療法増強効果をもたらす事が示唆されている．そこで，40-41°C前後の低温度加温を加温目標に定めるならば，患者の負担も軽減し，体勢保持も確保され，治療中断を避ける事も可能となる．腫瘍内休止期細胞分画への効果に着目し，化学療法や化学放射線療法に併用された MTH の有用性も明らかにされている．温熱併用放射線治療においては，42-43°C以上の加温が保証されるならば，温熱治療は放射線照射後に施行されるべきであるが，42°C以上の加温が困難であるならば，放射線照射と加温の順序を逆転させ，腫瘍酸素化効果を誘導する MTH 後に放射線照射を施行し，放射線増感効果を臨床的に期待するのも有用であろうと考えられる．