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ROLE OF HYPERTHERMIA, IN COMBINED TREATMENT OF CANCER

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ABSTRACT
Hyperthermia, the procedure of raising the temperature of tumour-loaded tissue to 40–43°C, is applied as an adjunctive therapy with various established cancer treatments such as radiotherapy and chemotherapy. The potential to control power distributions in vivo has been significantly improved lately by the development of planning systems and other modelling tools. This increased understanding has led to the design of multiantenna applicators (including their transforming networks) and implementation of systems for monitoring of E-fields (eg, electro-optical sensors) and temperature (particularly, online magnetic resonance tomography). Hyperthermia (HT) is one of the hot topics that have been discussed over decades. However, it never made its way into primetime. The basic biological rationale of heat to enhance the effect of radiation, chemotherapeutic agents, and immunotherapy is evident. Preclinical work has confirmed this effect. HT may trigger changes in perfusion and oxygenation as well as inhibition of DNA repair mechanisms. Moreover, there is evidence for immune stimulation and the induction of systemic immune responses. Despite the increasing number of solid clinical studies, only few centers have included this adjuvant treatment into their repertoire. However, for every particular temperature-dependent interaction exploited for clinical purposes, sophisticated control of temperature, spatially as well as temporally, in deep body regions will further improve the potential.

KEYWORDS: Hyperthermia, Mechanism, Radiotherapy, Chemotherapy, Immunotherapy.

INTRODUCTION
Hyperthermia (HT) is defined as an exogenous, supraphysiological elevation of tissue/body temperature. The beginning of modern HT dates back to the 1700s when remissions of malignant tumors were repeatedly associated with concomitant bacterial infections. This effect was first systematically investigated at the break of the 19th century by Coley.[1] Patients with unresectable sarcomas received injections of bacterial vaccines for fever induction. In total, a cure rate of 20% was achieved.[2] It took several decades of technological developments for local/locoregional heat application until HT alone became available for clinical application.

Nowadays, HT is either administered independently or, more often, in combination with radiotherapy (RT) or chemotherapy (CT). HT alone is being used for direct ablation of single tumor lesions with temperatures exceeding 50°C. Multiple techniques are being used to obtain necessary temperature coverage such as high-intensity focused ultrasound and radiofrequency-, microwave-, or infrared laser-based heating *via* ablation catheters directly inserted into the tumor.[3] In bimodal treatment schemes such as thermoradiotherapy (RTHT) and chemoradiotherapy (RTCT) as well as in trimodal thermochemoradiotherapy (RTHTCT), HT is utilized for augmentation of treatment effects of the concomitant oncological therapy. Necessary tissue temperatures are significantly lower ranging from 39 to 43°C.[4,5] In this literature-based review, a brief introduction to HT physiology, cell biology, and immune response is given to examine the underlying modes of action of HT. Currently used HT techniques for heat delivery and temperature control are described. The clinical evidence of combining RT with HT is summarized and sorted per tumor entity. To this end, a PubMed search was conducted searching for the term “hyperthermia” in combination with tumor entities treatable by RT, and terms describing technical aspects such as “biology,” “physiology,” “chemotherapy,” and “radiation therapy.” Special emphasis is given to recent meta-analyses and published prospective trials.

Hyperthermia is often used in combination with chemotherapy and radiotherapy for cancer treatment. Recently, immunotherapy has become a popular research area, breaking exciting new ground with concurrent immunotherapy and hyperthermia. Much evidence has demonstrated the effectiveness of multidisciplinary synergistic therapy, and the underlying mechanism has been gradually explored. In this review, we focus on the mechanism of various cancer treatments in the current

literature and recent advances in hyperthermia. Additionally, we review clinical studies of hyperthermia combined with other therapies in the previous 10 years and propose future prospects for hyperthermia in multidisciplinary synergistic therapy.

Hyperthermia refers to the use of heat and its secondary effects produced by raising the temperature of the whole body and/or local tumor tissue to treat malignant tumors. In clinical practice, it can be used alone or in combination with other methods such as radiotherapy (RT), chemotherapy, and immunotherapy. Hyperthermia is mainly divided into 3 categories according to the manner of administration: local, regional, and whole-body hyperthermia. Local hyperthermia is defined as increasing the temperature of local tumors and is often used for skin or natural body surface tumors, such as cervical lymph node metastases and skin tumors. Regional hyperthermia is achieved by increasing the perfusion of organs or limbs with heated liquid, such as intraperitoneal hyperthermia, which is often combined with chemotherapy, and radiofrequency in deep tumors. Whole-body hyperthermia is mostly applied to treat metastatic tumors.[1] According to different heating media, it can be divided into microwave heating therapy, infrared heating therapy, magnetic heating therapy, and photothermic therapy, among others.[2] Although increasing studies are focusing on the mechanism of hyperthermia, many details still remain unclear. At present, hyperthermia is widely used in the clinic, but how to achieve a more appropriate target temperature, more accurate target location, and an optimal treatment strategy remain a great challenge.

Methods to increase temperatures

To reach temperatures clearly above the systemic temperature of 37·5°C in a defined target volume is a technical challenge and still under development.[1] The temperature increase is induced by applying a power-density specific absorption rate (SAR; measured in W/kg). Human basal metabolic rate (basal metabolism) is above 1 W/kg. Perfusion counteracts the temperature rise. Perfusion rates in human tumours are around 5–15 mL per 100 g per min, but they vary widely. To reach therapeutic temperatures of about 42°C at least in some parts of such tumours necessitates power density of about 20–40 W/kg at the target region.At present, the optimum temperature distribution for clinical purposes is unknown. Temperature distributions achieved to date have limited absolute values and homogeneity (minimum temperatures typically lie between 39·5°C and 40·5°C), mainly because of physical and physiological characteristics such as electrical tissue boundaries, local perfusion variations, and perfusion regulations. Only about 50% of deeply located tumours reach at least 42°C at one particular measurement point. Clinical studies have shown that uncritical adoption of preclinical results into clinical guidelines for tumour temperatures is not justified. Nevertheless, many phase II clinical studies have shown associations between tumour response and characteristics of temperature distribution (minimum temperature or minimum thermal dose in the tumour area).[2] Even though the tumour temperatures that have to be reached for clinical efficacy are still unclear, we should achieve temperature distributions as high and homogeneous as possible. Technological potential for in vivo monitoring and control of temperature distribution has not yet been intensively scrutinised, at least for the regional hyperthermia approach.

Local hyperthermia

Superficial tumours can be heated by means of antennas or applicators emitting mostly microwaves or radiowaves placed on their surfaces with a contacting medium. Several types of applicators have been used clinically, such as waveguide applicators, horn, spiral, current sheet, and compact applicators. The main components of such a hyperthermia system. The electromagnetic coupling of the applicator to the tissue is ensured by a water bolus (preceding water path). Intratumoral temperature can be controlled by the output of the power generator or by positioning the applicator. The resulting SAR distribution is subject to strong physical curtailment resulting in a therapeutic depth of only a few centimetres and is even further limited in regions with an irregular surface, such as the head and neck area, the supraclavicular region, or the axilla. Quality-assurance guidelines have been developed for local hyperthermia. Commercially available electromagnetic applicators have a typical emitting diameter of 15 cm at a frequency of 150-430 MHz with therapeutic depths not more than 3 cm. Dual or multiapplicator operation would be better, but these techniques have been developed in only a few specialised centres and are not commercially available. Ultrasound applicators offer better physical features with a wandering focus, but cause discomfort, and are thus at present of less practical importance.

Interstitial and endocavitary hyperthermia for this procedure, antennas or applicators are implanted within the tumour, and in most cases a heat treatment is administered in combination with brachytherapy by the afterloading method in close connection to the area to be heated. This technique is suitable for tumours that are less than 5 cm in diameter, but mainly in any location feasible for implantation (eg, head and neck, prostate).[2] Various antenna types are available, including microwave antennas, radiofrequency electrodes, ultrasound transducers, heat sources (ferromagnetic seeds, hot water tubes), and laser fibres. For physical reasons, the power-density gradient of the antenna surroundings is so high that variability in temperature is generally greater than with local hyperthermia. To ensure therapeutic temperatures at all points of the target volume requires a distance between adjacent applicators of not more than 1·0–1·5 cm. But such close positioning is very invasive. Furthermore, positioning and orientation of microwave antennas can be critical because of their sensitivity to interference. Applicators

functioning according to the hot-source principle require an even smaller distance between them.

Regional hyperthermia and part-body hyperthermia

Deep-seated tumours-eg, of the pelvis or abdomen can be heated by arrays of antennas. The Sigma-60 applicator is a widely spread applicator, which consists of four dipole antenna pairs arranged in a ring around the patient. Planning systems describe correctly to some extent the power-density and temperature distribution depending on various treatment variables. Even though each antenna pair can be controlled in phase and amplitude, there are restrictions in terms of the generated SAR distribution.[3]

Whole-body hyperthermia

In carcinomas with distant metastases, a steady state of maximum temperatures of 42°C can be maintained for 1 h with acceptable adverse effects. Such a procedure can be achieved only with deep analgesia and sedation or general anaesthesia. Whether intubation is required for safe administration is still a matter of discussion.[4,5] A completely different range of toxic effects arises from the systemic stress in interaction with the various anaesthesia methods applied compared with locoregional methods. The basal metabolic rate of a patient weighing about 70 kg is 85 W at 37°C and double that at 42°C; this in itself is enough to raise the body temperature within 180 min from 37·5°C to 42·0°C, if thermal isolation is perfect. Since the early 1980s there have been many clinical efforts to shorten the preheating time. Various methods (pyrogens, extracorporeal heating, contact heating) were abandoned because of unacceptable toxic effects and limited effectiveness. Today, only radiant systems are in clinical use, with typical preheating times of 60–90 min (from 37·5°C upwards).[6]

Hyperthermic isolated limb perfusion

The isolated hyperthermic perfusion of limbs is based on bypassing a large supplying artery and a limb-draining vein—for example, the iliac artery and vein for the lower extremities. Since this surgical procedure is long established, hyperthermic perfusion with extracorporeal heat exchange is technically straightforward. Compared with whole-body hyperthermia, systemic side-effects are less, leading to early clinical application. Variables influencing the therapeutic ratio are, besides the temperature, the cytostatic drug concentration (higher concentrations are applied than in systemic therapy), the flow rate (30–40 mL/min), and the composition of the perfusing fluid (packed-cell volume, pO2, pH).[7,8]

Mechanisms of hyperthermia

Hyperthermia is a therapy that consists of heating the lesion site to treat tumors based on the differential response of tumor tissue and normal tissue to heat. Blood vessels in the tumor are different from those in normal tissues. The normal vascular system is a network of arterioles, capillaries, and veins. In contrast, tumor blood vessels assemble into a chaotic network of capillaries, most of which lack smooth muscle layer and innervation. This vascular abnormality leads to a hypoxic environment inside the tumor, and a mild temperature (37°C to 42°C) can lead to local vascular dilation and increased vascular perfusion to improve oxygenation of tumors, thus mitigating inflammation and deep tissue hyperemia, moreover reducing the excitability of pain-sensing nerves to relieve pain.[9] At temperatures above 42°C, the tumor vasculature is directly damaged by increased permeability, which results in fluid and protein accumulation in the microenvironment and contributes to elevated interstitial fluid pressure, in turn leading to vessel compression and further vascular perfusion reduction. Furthermore, the mechanism responsible for the vascular injury is activated, and tumor growth and proliferation are inhibited during the heating process. In addition, when the temperature exceeds 37°C, the membrane fluidity increases, thereby affecting its permeability. Changes in the cytoskeleton and membrane structure can destroy the tumor cell movement, intracellular signal transduction, and further inhibit tumor growth and metastasis.[10]

Mechanisms of hyperthermia combined with chemotherapy

The combination of hyperthermia and chemotherapy agents can lead to an overall enhancement of drug cytotoxicity. An artificial increase in tissue temperature can lead to higher fluidity of the bilayer of phospholipids in tumor cells, which in turn facilitates their drug permeability.[11] Moreover, the structure of the cell membrane changes, the membrane viscosity decreases, and cellular uptake of drugs rises in cancer tissue. Studies have demonstrated that hyperthermia (43°C) has a synergistic interaction with cisplatin (cPt) on cell growth inhibition, probably because it can modulate the function of the cPt transporter Ctr1, leading to increased cPt uptake with enhanced cytotoxicity. Carboplatin and oxaliplatin show only additive effects. Based on the above-mentioned mechanisms, regional chemotherapy combined with hyperthermia has been developed, such as hyperthermic intraperitoneal chemotherapy (HIPEC) or hyperthermic intravesical chemotherapy (HIVEC) of the bladder, in which heated chemotherapy agents are perfused into the abdominal cavity or bladder to exert antitumor effects by increasing their thermodynamic effects.[12]

Mechanisms of hyperthermia combined with radiotherapy

Hyperthermia increases the sensitivity of tumor cells to ionizing radiation. First, it is well known that hypoxia is related to radioresistance, and improvement of the hypoxic environment of tumor tissues can lead to increased radiosensitivity of tumors. This phenomenon can be attributed to the ability of hyperthermia to reoxidize hypoxic tumor cells by increasing blood flow, so that tumor cells lose the protection of the hypoxic environment during RT. Only an appropriate temperature can improve oxygenation and vascular perfusion of

tumors, resulting in radiosensitization. In contrast, a high temperature will reduce blood perfusion, damage blood vessels, and aggravate cell hypoxia, which is associated with decreased radiosensitivity.[13] Changes in protein structure caused by heat can affect multiple components of cells to varying degrees, thus suppressing DNA damage repair. Hyperthermia induces heat shock protein (Hsp) 70 synthesis and thus interferes with telomere activity. Overexpression of telomerase in tumor cells can stabilize telomeres and prolong the life of cells. Therefore, hyperthermia indirectly inhibits the activity of telomerase and promotes cancer cell apoptosis. The sensitivity of tumor cells to ionizing radiation is influenced by their phases of the cell cycle. G0 and S phase cells are less sensitive to RT injury but more sensitive to hyperthermia. Furthermore, RT can reduce the thermal tolerance of tumor cells and improve the curative effect of hyperthermia.[14]

Mechanisms of hyperthermia combined with immunotherapy

Studies have also revealed the role of temperature in facilitating the efficacy of immunotherapy. Accumulating evidence indicates that the immunosuppressive state of the tumor microenvironment is supported by hypoxia within tumors.[15] Using the potential ability of heat to modulate reoxygenation of the targeted tumor site plays a fundamental role when coupled with immunotherapy. Furthermore, an elevated temperature can not only induce the immune response at the targeted tumor site, but it can also stimulate an antitumor response throughout the body.

Hyperthermia combined with chemotherapy

Hyperthermia combined with chemotherapy is widely used in clinical practice and has been widely studied in soft tissue sarcoma (STS). In a retrospective study, 61 cases of high-grade STS patients were included, among whom 28 received preoperative neoadjuvant chemoradiotherapy (CRT) and 33 received neoadjuvant chemotherapy plus hyperthermia (HCT). Hyperthermia aiming at a target temperature of 42°C was usually conducted on the first and third days of chemotherapy for 60 minutes, with isocyclophosphamide applied during or immediately after local hyperthermia.[16] There were no significant differences in tumor response between the 2 groups (P = .67), whereas for toxic reactions, postoperative wound dehiscence and complications in the CRT group were markedly higher than in the HCT group. Furthermore, there were no significant differences in overall survival (OS), local control, and freedom from distant metastases over 2 years between the 2 groups.

In the safety evaluation, the combined treatment group did not show an increased incidence of adverse reactions of chemotherapy.[17] Therefore, this trial demonstrated that local hyperthermia could improve the efficacy of chemotherapy for high-risk localized STS. In addition, subgroup analysis revealed a greater benefit in the patients who underwent surgical resection. Despite some problems in the above-mentioned clinical trials, for example, the combined treatment group received more chemotherapy than the chemotherapy alone group; this is the first phase III clinical trial to investigate whether chemotherapy combined with hyperthermia or chemotherapy alone is more effective in patients with STS. To some extent, the results have indicated that the combination of hyperthermia and other therapies is a good therapeutic strategy, but the timing of hyperthermia combined with chemotherapy and the method of hyperthermia require further experimental study.[18]

Regional inductive moderate hyperthermia in combination with chemotherapy can improve the therapeutic effect of breast cancer patients with multiple liver metastases. The Mega Therm apparatus was set in the metastatic lesion to generate electromagnetic irradiation, with a temperature less than 40°C lasting for 30 minutes. The magnetic field generated during regional inductive moderate hyperthermia can significantly accelerate the interaction between chemical molecular oxygen and cellular metabolites, leading to remarkably enhanced oxidative stress in tumors and their microenvironments and increased apoptosis induced by hyperthermia. For advanced ovarian and colorectal cancers, extensive peritoneal metastasis is often a sign of a poor prognosis.[19] Among these patients, peritoneal recurrence is a major problem. Owing to the high selectivity of intraperitoneal administration and the pharmacokinetic characteristics of local chemotherapy, a positive effect of HIPEC on the survival of patients with advanced ovarian and colorectal cancer has been reported with increasing frequency. HIPEC is a local treatment to clean the abdominal cavity with hyperthermic chemotherapeutic drugs, which is based on the direct cytotoxicity of heat to cancer cells and the indirect increase in the toxicity of anticancer drugs. Moreover, HIPEC must be combined with complete surgical resection of peritoneal cancers There is increasing evidence that HIPEC is beneficial for the prognosis of ovarian peritoneal metastasis. In a multicenter retrospective study, 56 cases of recurrent epithelial ovarian cancer patients who were treated with cytoreductive surgery combined with HIPEC were included.[20]

Therefore, regional hyperthermia is often used in combination with chemotherapy, generally not alone, in patients with advanced nonoperative tumors.[21] Regional hyperthermia is usually given on the first and last day of the chemotherapy cycle for 60 minutes at 40°C to 42°C.

Hyperthermia combined with radiotherapy

Hyperthermia alone or combined with RT has special significance in the treatment of locally advanced cervical cancer. Evidence has shown that hyperthermia can improve the survival and reduce toxicity in patients with locally advanced cervical cancer.[22] In 2000, the *Lancet* published a Dutch Deep Hyperthermia Group trial, which was designed to treat locally advanced pelvic

tumors with RT alone or combined with hyperthermia. Hyperthermia was prescribed 1 to 4 hours after RT once weekly, for a total of 5 times. Treatment was continued for 60 minutes after the tumor reached 42°C, usually up to 90 minutes. This multicenter phase III trial showed that the 3-year survival rate nearly doubled from 27% to 51% in patients with locally advanced cervical cancer after combining RT with hyperthermia. Therefore, for patients with locally advanced cervical cancer, the combination of hyperthermia and RT should be considered to improve the therapeutic effect. Not only does the temperature of the hyperthermia contribute to the effectiveness of the treatment, but the timing also matters.[23]

Concerning head and neck tumors, RT is the main treatment, but only 20% of patients with locally advanced recurrent head and neck tumors can be treated with surgery or re-irradiation therapy, and the disease control rate after retreatment is only 26% to 52%. Although the combination of RT and chemotherapy improved survival, toxicity was increased.[70] However, there is growing evidence indicating that heat improves the prognosis of head and neck tumors. Huilgol et al reported a phase III clinical trial in which 56 patients with locally advanced head and neck cancer were randomly admitted for RT either with (n = 28) or without (n = 26) regional hyperthermia. The complete response rate of the RT-alone group and the combination group were 42% and 79% ($P < .05$), respectively, and no obvious toxicity reaction was observed.[24]

Radiotherapy is often combined with deep hyperthermia, mostly for head and neck tumors and other radiosensitive malignant tumors. Hyperthermia is often carried out in the interval of RT, usually 1 to 2 hours after RT, with the temperature reaching 42°C and lasting for 60 to 90 minutes. Special devices are often required to achieve deep hyperthermia. For example, the HYPERcollar applicator was invented and improved continuously to achieve deep local head and neck hyperthermia, with verified therapeutic effects in multiple studies.[25]

Hyperthermia combined with chemo radiotherapy

Hyperthermia often increases sensitivity to conventional chemo radiotherapy in some tumors that were previously less sensitive to chemo radiotherapy alone. The combination of hyperthermia and chemo radiotherapy has been widely studied in bladder and rectal cancer, among others.[26]

In 2009, Wittlinger et al published a retrospective study of 45 patients with high-risk T1 and T2 stage bladder cancer. After transurethral resection, the patients received whole bladder and pelvic lymph node RT for 5 consecutive days a week and regional deep hyperthermia (RHT) once a week. RT was started within 60 minutes after RHT. During the whole course of RT, the lowest and highest frequencies of hyperthermia treatment were 5 and 7 times, respectively. Moreover, cPt combined with 5-fluorouracil chemotherapy was scheduled for the first and fifth weeks of treatment, and cPt was also applied to RHT.[27] The median follow-up was 34 months (range = 12-60), and the complete response rate was 96% (43/45). The 3-year local recurrence-free survival rate was 85%, OS rate was 80%, disease-specific survival rate was 88%, metastasis-free survival rate was 89%, and bladder-preserving rate was 96% (43/45). Overall, the patients were satisfied with their quality of life. In clinical practice, RHT combined with radio chemotherapy has been shown to be an effective sensitizer for chemo radiotherapy, which can be applied in various types of tumors. Chemo radiotherapy is carried out according to clinical guidelines, while hyperthermia is usually performed immediately after RT, once or twice a week. Chemotherapeutic drugs are infused into the body during the hyperthermia process. In addition, the regional temperature should be monitored continuously during heating. After reaching the target temperature, hyperthermia should be carried on for at least 60 minutes and not exceed 90 minutes. Typically, the temperature achieved in 90% of tumor-related measurement points (T90) and the cumulative equivalent minutes at a reference temperature of 43°C (CEM T43) serve as effective indices.[28]

Hyperthermia combined with immunotherapy

In recent years, immunotherapy has been widely praised, but its curative effect is still limited by tumor immune escape. Tumor immune escape refers to tumor cells that can avoid recognition and attack by the immune system by changing themselves or their microenvironment. The complex network of the tumor microenvironment significantly weakens the efficacy of immunotherapy, making it difficult to initiate immunotherapy in solid tumors.[29] A crucial feature of the microenvironment that promotes tumor immune escape is the lack of tumor antigen recognition and antitumor T-cells. Recent studies have shown that immunotherapy is more effective when performed in combination with other therapeutic approaches. In 2018, Kleef et al reported a 50-year-old woman with advanced triple-negative breast cancer who had postoperative axillary lymph node metastasis and even bilateral lung metastasis after standard RT. The gene analysis revealed wild-type BRCA1, with a 61% Ki-67 index, suggesting a high proliferation potential. The patient received a combination of low-dose checkpoint inhibitors, nivolumab (0.5 mg/kg) and ipilimumab (0.3 mg/kg), accompanied by local hyperthermia once a week, over 3 weeks, and high-dose interleukin-2–induced whole-body hyperthermia for 5 days. After 1 year of treatment, the total gene expression in the resected metastatic lymph node showed that immune surveillance was enhanced, with several overexpressed checkpoint genes and active cytokines (eg, interleukin-2, interferon-γ, transforming growth factor-β, etc). Overall, the patient was completely relieved, presenting with only temporary Health Organization Grades I-II diarrhea and skin rash, and the

OS period was 27 months from the beginning of treatment.[30]

CONCLUSION

At present, hyperthermia has been widely used in clinical practice, and it has achieved good efficacy in clinical trials examining a variety of malignant tumors. Moreover, many researchers have tended to explore the combination of hyperthermia and other therapies. Hyperthermia plays an antitumor role by killing cells directly, increasing drug permeability, enhancing radiosensitivity, disrupting DNA repair, releasing antigens, and activating immunity. The key parameters of hyperthermia are the temperature and heating time, and therefore, real-time multipoint temperature measurement is crucial. Currently, conventional local hyperthermia is usually carried out for 60 to 90 minutes at a target temperature of 39.5°C to 43°C, while whole-body hyperthermia often lasts for no less than 90 minutes at 39.5°C to 42°C. In addition, considering individual differences, the duration of hyperthermia should be appropriately extended at a lower temperature for patients with poor tolerance, whereas for patients with good tolerance, the duration can be appropriately shortened at a higher temperature. With the increase in temperature, the optimal antitumor immune effect can be achieved only in a narrow thermal dose range. Nevertheless, it is still a great challenge to apply appropriate and sufficient heat energy to the target tumor without affecting normal tissue and accurately detect the temperature of the target position in vivo. Additionally, more data are needed to help guide the clinical practice of hyperthermia, such as how to combine it with other therapies, the sequence, and the interval between therapies, among others.

REFERENCES

1. Hand JW. Technical and clinical advances in hyperthermia treatment of cancer. In: Lin JC, ed. Electromagnetic Interaction With Biological Systems. Boston, MA: Springer, 1989; 59-80.
2. Van der Zee J. Heating the patient: a promising approach? Ann Oncol, 2002; 13: 1173-1184.
3. Bicher HI, Hetzel FW, Sandhu TS, et al. Effects of hyperthermia on normal and tumor microenvironment. Radiology, 1980; 137: 523-530.
4. Vaupel P, Kallinowski F. Physiological effects of hyperthermia. Recent Results Cancer Res., 1987; 104: 71-109.
5. Shchors K, Evan G. Tumor angiogenesis: cause or consequence of cancer? Cancer Res., 2007; 67: 7059-7061.
6. Brizel DM, Dodge RK, Clough RW, Dewhirst MW. Oxygenation of head and neck cancer: changes during radiotherapy and impact on treatment outcome. Radio Oncol, 1999; 53: 113-117.
7. Fajardo LF, Schreiber AB, Kelly NI, Hahn GM. Thermal sensitivity of endothelial cells. Radiat Res., 1985; 103: 276-285.
8. Reinhold HS, Endrich B. Tumour microcirculation as a target for hyperthermia. Int J Hyperthermia, 1986; 2: 111-137.
9. Jain S, Purohit A, Nema P, Vishwakarma H, Qureshi A, kumar Jain P. Pathways of Targeted Therapy for Colorectal Cancer. Journal of Drug Delivery and Therapeutics, Sep 14, 2022; 12(5): 217-21.
10. Meyer RE, Braun RD, Rosner GL, Dewhirst MW. Local 42°C hyperthermia improves vascular conductance of the R3230Ac rat mammary adenocarcinoma during sodium nitroprusside infusion. Radiat Res., 2000; 154: 196-201.
11. Song CW, Park HJ, Lee CK, Griffin R. Implications of increased tumor blood flow and oxygenation caused by mild temperature hyperthermia in tumor treatment. Int J Hyperthermia, 2005; 21: 761-767.
12. Purohit A, Jain S, Nema P, Vishwakarma H, Jain PK. Intelligent or smart polymers: advance in novel drug delivery. Journal of Drug Delivery and Therapeutics, Sep 15, 2022; 12(5): 208-16.
13. Wallner KE, Degregorio MW, Li GC. Hyperthermic potentiation of cis-diamminedichloroplatinum(II) cytotoxicity in Chinese hamster ovary cells resistant to the drug. Cancer Res., 1986; 46(12 pt 1): 6242-6245.
14. Landon CD, Benjamin SE, Ashcraft KA, Dewhirst MW. A role for the copper transporter Ctr1 in the synergistic interaction between hyperthermia and cisplatin treatment. Int J Hyperthermia, 2013; 29: 528-538.
15. Owusu RA, Abern MR, Inman BA. Hyperthermia as adjunct to intravesical chemotherapy for bladder cancer. BioMed Res Int., 2013; 2013: 262313.
16. Passot G, Cotte E, Brigand C, et al. Peritoneal mesothelioma: treatment with cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy [in French]. J Chir (Paris), 2008; 145: 447-453.
17. Seegenschmiedt MH, Fessenden P, Vernon CC. Thermoradiotherapy and Thermochemotherapy. Berlin, Germany: Springer, 1995.
18. Kaur P, Hurwitz MD, Krishnan S, Asea A. Combined hyperthermia and radiotherapy for the treatment of cancer. Cancers (Basel), 2011; 3: 3799-3823.
19. Jain S, Kirar M, Bindeliya M, Sen L, Soni M, Shan M, Purohit A, Jain PK. Novel drug delivery systems: an overview. Asian Journal of Dental and Health Sciences, Mar 15, 2022; 2(1): 33-9.
20. Durante M, Gialanella G, Grossi GF, et al. Radiation-induced chromosomal aberrations in mouse 10T1/2 cells: dependence on the cell-cycle stage at the time of irradiation. Int J Radiat Biol., 1994; 65: 437-447.
21. Sitkovsky MV. T regulatory cells: hypoxia-adenosinergic suppression and re-direction of the immune response. Trends Immunol, 2009; 30: 102-108.
22. Sitkovsky M, Lukashev D. Regulation of immune cells by local-tissue oxygen tension: HIF1 alpha and

adenosine receptors. Nat Rev Immunol, 2005; 5: 712-721.
23. Vega VL, De Maio A. Increase in phagocytosis after geldanamycin treatment or heat shock: role of heat shock proteins. J Immunol, 2005; 175: 5280-5287.
24. Goldring CE, Reveneau S, Chantome A, et al. Heat shock enhances transcriptional activation of the murine-inducible nitric oxide synthase gene. FASEB J., 2000; 15: 2393-2395.
25. Slawinska A, Hsieh JC, Schmidt CJ, Lamont SJ. Heat stress and lipopolysaccharide stimulation of chicken macrophage-like cell line activates expression of distinct sets of genes. PLoS One., 2016; 11: e0164575.
26. Ichiyanagi T, Imai T, Kajiwara C, et al. Essential role of endogenous heat shock protein 90 of dendritic cells in antigen cross-presentation. J Immunol, 2010; 185: 2693-2700.
27. Imai T, Kato Y, Kajiwara C, et al. Heat shock protein 90 (HSP90) contributes to cytosolic translocation of extracellular antigen for cross-presentation by dendritic cells. Proc Natl Acad Sci U S A., 2011; 108: 16363-16368.
28. Purohit A, Jain S, Nema P, Jain DK, Vishwakarma H, Jain PK. A comprehensive review on tailoring an herbal approach for treatment of poly cystic ovarian syndrome. Asian Journal of Dental and Health Sciences, Mar 15, 2022; 2(1): 27-32.
29. Tanaka T, Okuya K, Kutomi G, et al. Heat shock protein 90 targets a chaperoned peptide to the static early endosome for efficient cross-presentation by human dendritic cells. Cancer Sci., 2015; 106: 18-24.
30. Knippertz I, Stein MF, Dörrie J, et al. Mild hyperthermia enhances human monocyte-derived dendritic cell functions and offers potential for applications in vaccination strategies. Int J Hyperthermia., 2011; 27: 591-603.