
CURRENT UNDERSTANDING OF MODULATED ELECTRO-HYPERTHERMIA IN CANCER TREATMENT

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Traditional hyperthermia involves increasing the temperature at the tumor site above 39°C, including death in cancer cells. Although hyperthermia is an effective cancer treatment, its clinical application has decreased due to potential complications, including damage to surrounding normal tissue. In recent years, modulated electro-hyperthermia (mEHT) has emerged as an effective and safe treatment modality. mEHT selectively heats tumor cells to 42–43°C, while reducing the average temperature in the treatment area, including the surrounding normal tissue, compared to conventional methods. Additionally, mEHT may be used in combination with systemic chemotherapy and radiation therapy in tumor treatment, providing a synergistic effect to increase efficacy. As chemotherapy and radiation therapy technologies advance, the application of combined mEHT may improve clinical outcomes. In this study, we review and discuss reports on the clinical outcomes of mEHT combined with chemotherapy and/or radiation therapy, which are established anticancer treatments.

KEYWORDS: Hyperthermia; Modulated electro-hyperthermia; Neoplasms; Therapeutics

INTRODUCTION

Standard cancer treatment consists of surgery, chemotherapy, and radiation therapy, either alone or in combination [1–3]. Of these, systemic chemotherapy and radiation therapy duration range from several weeks to several months, and takes at least several weeks to confirm the clinical outcomes. If the tumor size increases during follow-up after chemotherapy and/or radiation therapy, the prognosis is poor. Therefore, an effective combined therapy that enhances the efficacy of chemotherapy and radiation therapy can significantly improve clinical outcomes. Recently, modulated electro-hyperthermia (mEHT), which can selectively maintain tumor cells at 42–43 °C using a high-frequency electromagnetic field (13.56 MHz) to the lesions, has been proposed as a promising combined modality therapy [4,5]. This technique operates based on a complex energy dose control paradigm rather than a straightforward temperature concept. The main targets of mEHT are the intercellular components and cell membranes of tumor tissues, and it acts selectively on malignant tumor cells with little damage to normal cells [4–6]. mEHT induces tumor cell death by increasing blood flow, suppressing hypoxia, and inhibiting DNA repair in tumors [7,8]. Additionally, when combined with systemic therapy, mEHT can enhance drug concentration within the lesion and increase the sensitivity of chemotherapy and radiation therapy [9,10]. Therefore, mEHT is a promising treatment that can be used in combination with systemic therapy and radiation therapy. This study reviews the clinical outcomes of mEHT in conjunction with chemotherapy and/or radiation therapy [11,12].

MEHT MECHANISM

Conventional hyperthermia aims to directly kill cancer cells by using temperatures above 39 °C, but this approach has several drawbacks. First, the heterogeneous nature of tumors makes it challenging to deliver and maintain uniform thermal energy [13]. Second, thermal damage causes severe complications to the tumor-surrounding tissue. Third, as temperatures rise above 43 °C, blood flow within the tumor decreases, potentially reducing the effectiveness of chemotherapy and/or radiation therapy [14]. Consequently, mEHT has emerged as an innovative method (Fig. 1). It selectively delivers thermal energy only to the tumor cell membrane and extracellular matrix, using temperatures below 43 °C, thereby minimizing the impact on surrounding tissues and addressing

the limitations of traditional hyperthermia. mEHT selectivity for cancer cells was confirmed in vitro, and severe malignancy increases the degree of damage caused by mEHT [6]. Among the biological effects of mEHT, the most clinically useful are improving the perfusion and oxygenation conditions and interfering with the DNA repair mechanism of tumors [15–17]. Based on these characteristics, mEHT is being used as a combined therapy to enhance the effects of chemotherapy and radiation therapy.

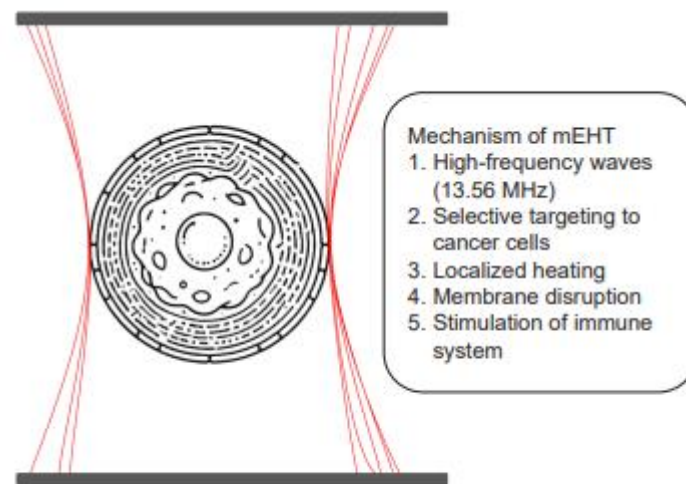


Fig. 1. Mechanism of modulated electro-hyperthermia (mEHT).

MEHT IN COMBINATION WITH RADIATION THERAPY

Theoretically, mEHT is an excellent radiosensitizer. Conventional radiation therapy often causes hypoxic regions within tumors during treatment [18]. mEHT can not only increase tumor perfusion and oxygen supply, but also increase the tumor apoptotic effect of hyperthermic cells themselves on hypoxic cells, leading to improved efficacy of radiation therapy [19,20]. In addition, the local control rate could be improved by suppressing DNA repair in tumor cells by radiation therapy [20,21]. Since hyperthermia is highly effective on S phase cells, which are resistant to radiation therapy from a cell cycle perspective, concurrent therapy is more effective [22]. mEHT is a useful combined treatment to consider for cancer types that are highly resistant to radiation therapy. The prescribed dose is limited by the tolerance of the critical normal tissue surrounding the radiation treatment site, making hyperthermia highly necessary in cases of radiation retreatment. Since radiation continues to affect lesions even after treatment termination, mEHT could be highly effective in sequential treatments within several months post-radiation therapy. However, there is little information on this, and further study is needed.

MEHT IN COMBINATION WITH CHEMOTHERAPY

mEHT increases blood flow and permeability, contributing to an environment that is conducive to drug delivery to tumors [7]. Owing to the effects of mEHT on tumor cells, including cell membrane damage and increased intratumoral stress, cancer cells compromised by this process may become even more susceptible to chemotherapy [23].

Based on these theoretical foundations, studies on clinical outcomes where hyperthermia was combined with systemic chemotherapy for various cancer types have demonstrated improved clinical results [24–26]. In clinical practice, we often encounter cases where reduced doses of chemotherapy are necessary for patients with poor performance status due to advanced age or concomitant diseases, or for patients who experience severe side effects from chemotherapeutic agents. We believe that mEHT is an effective combination treatment option that can compensate for reduced doses of chemotherapy.

SAFETY OF MEHT

mEHT uses a heating temperature of approximately 42°C, which is lower than that used in conventional hyperthermia treatments, and side effects from heat exposure are relatively few and minor [27]. A common complication from heat exposure is mild erythema in the skin adjacent treated area [5]. Although it is rare, skin burns can occur if the heat power is intense or not properly monitored. In addition to the potential for thermal damage to the surrounding normal tissue at the treatment site, there is an occasional risk of fat necrosis due to minor damage to subcutaneous adipose tissue [28]. Some patients experience mild discomfort, pain, or a burning sensation during or after treatment due to local heating, but most recover without any intervention. Currently, serious side effects from mEHT alone are very rare, although minor side effects may occur. Since these side effects can be managed and minimized through careful supervision by the treating physician, the authors recommend treatment in an outpatient clinic at least once a week. Regarding systemic symptoms, hyperthermia can cause fatigue and tiredness, particularly when used in conjunction with chemotherapy or radiation therapy. Overall, most side effects associated with hyperthermia are manageable in clinical practice or are minor enough for patients to tolerate. Hyperthermia therapy has an antitumor effect on its own, but it is primarily used as a cancer treatment with the expectation of a synergistic effect when combined with chemotherapy and radiation therapy. Therefore, whether the incidence of serious side effects changes when hyperthermia is administered in combination with chemotherapy and radiation therapy is a crucial factor in determining clinical treatment strategies. Several studies have reported that mEHT has a low correlation with toxicity and demonstrates good safety [29–32]. A case report has claimed that hyperthermia helps maintain patient performance status and reduces chemotherapy toxicity [33]. However, several studies have reported an increased incidence of hematologic toxicity in patients who received hyperthermia, suggesting that hyperthermia may enhance the side effects of chemotherapy [34,35]. Although the safety of mEHT is higher than that of conventional hyperthermia [27], further evidence regarding toxicity associated with the treatment should be revealed through multiple well-designed randomized clinical trials.

PREVIOUSLY PUBLISHED STUDIES ON HYPERTHERMIA

A small number of randomized clinical trial and systematic review have been conducted using hyperthermia in patients with solid tumors, and the characteristics and oncological outcomes of these studies are summarized in Tables 1 and 2 [16,29,36–55]. Hyperthermia is regarded as an effective palliative treatment for cancer patients and can be utilized either as a monotherapy or in combination with other treatments. A randomized phase III trial by Chi et al. [55] demonstrated

that combining hyperthermia with radiotherapy in patients receiving palliative treatment for painful bone metastases extended the duration of pain relief and enhanced the overall pain control rate. Some studies have shown that hyperthermia enhances the therapeutic effect when combined with both chemotherapy and radiation therapy. The results of the EORTC 32961-ESHO 95 trial [47] suggest that for patients with localized high-risk soft tissue sarcoma, the combination of preoperative chemotherapy and hyperthermia is an effective treatment option. De Haas-Kock et al. [46] compared the efficacy of concurrent hyperthermia and radiation therapy with radiation therapy alone in the treatment of locally advanced rectal cancer. The results demonstrated that hyperthermia improved overall survival (hazard ratio, 2.06; 95% confidence interval [CI], 1.33–3.17; $p=0.001$), and increased complete tumor response rates (relative risk, 2.81; 95% CI, 1.22–6.45; $p=0.01$).

FUTURE DIRECTION

Hyperthermia may have an energy dose-dependent response, but little information is available on the appropriate dose or treatment schedule (twice a week vs. three times a week) that shows efficacy. It may vary depending on each cancer type, but also the combined treatment method. For example, in radiation therapy, conventional radiation regimens and stereotactic body radiation therapy show significant differences due to their unique treatment mechanisms; therefore, the optimal dose of mEHT to be combined should be explored. Since mEHT is a localized treatment, as with radiation therapy, the treatment dose may differ depending on the treatment site and limitations of treatment dose due to surrounding normal tissue; so well-designed studies must be carried out by dividing the tumor into each location.

Table 1. Summary of oncological outcomes and safety of hyperthermia in meta-analyses and systematic reviews

Author	Article type	Cancer type	Intervention	Total patients	Endpoints	Oncologic outcomes	Survival outcomes	QoL outcomes	Side effects
Datta et al. (2016) [36]	Meta-analysis	Breast	RT vs. HT+RT	627	CR	Improved CR with HT	-	-	Minimal acute and late morbidities
Hu et al. (2017) [39]	Meta-analysis	Esophagus	HT+CCRT vs. CCRT or RT alone	1,519	OS Long-term effects (LR and DM rate) Short-term effects (CR and TER)	HT+CCRT vs. CCRT: Improved CR (OR, 2.00; $p<0.00001$) and TER (OR, 3.47; $p<0.00001$) No difference in long-term effects HT+CCRT vs. RT alone: Higher CR (OR, 2.12; $p=0.003$) and TER (OR, 4.8; $p=0.002$) Lower LR (OR, 0.39; $p=0.0001$) and DM (OR, 0.46; $p=0.003$)	HT+CCRT vs. CCRT: Improved 1-, 3-, 5-, and 7-yr OS (OR 1.79, 1.91, 9.99, 9.49; $p<0.05$) HT+CCRT vs. RT alone: Improved 1-, 2-, 3-, and 5-yr OS (OR 3.20, 2.09, 2.43, 3.47; $p<0.05$)	-	HT+CCRT vs. CCRT: Less GI toxicities with HT (OR, 0.43; $p<0.00001$) HT+CCRT vs. RT alone: No statistical difference in toxicities
Van der Horst et al. (2017) [20]	Systematic review	Pancreas	HT+RT or CT or CCRT	395	Overall response rate OS	Improved overall response rate (43.9% vs. 35.3%)	Improved OS (11.7 mo vs. 5.6 mo)	-	-
De Haas-Kock et al. (2009) [46]	Systematic review	Rectum	HT+RT vs. RT alone	520	Pathologic CR OS Toxicity	Higher CR with HT (RR, 2.81; $p=0.01$)	Improved 2-yr OS (HR, 2.06; $p=0.001$) but, disappeared in 3-, 4-, 5-yr OS	-	No difference in acute toxicity
Veltsista et al. (2023) [48]	Systematic review	Soft tissue sarcoma	HT+CT or HT+RT	786/618	-	Increased RT effectiveness with HT	-	-	No significant toxicity of HT
Lutgens et al. (2010) [50]	Systemic Review	Uterine cervix	HT+RT vs. RT alone	487	CR LR OS Grade 3 to 4 acute and late toxicity	Improved CR (RR 0.56; $p<0.001$) and LR rate (HR 0.48; $p<0.001$)	Better OS (HR, 0.67; $p=0.06$)	-	No difference in acute or late grade 3–4 toxicity
Datta et al. (2016) [51]	Meta-analysis	Uterine cervix	HT+RT +/- CT vs. RT +/- CT	1,160	CR LC OS Acute and late grade 3/4 toxicity	Higher CR (+22.1%, $p<0.001$) and LC (+23.1%, $p<0.001$) with HT	No significant OS benefit	-	No difference in acute or late toxicities
Yea et al. (2021) [53]	Meta-analysis	Uterine cervix	HT+CCRT vs. CCRT	536	5-yr OS LRFs Acute and late toxicity	No LRFs benefit	Better 5-yr OS (HR, 0.67; $p=0.03$)	-	No difference in acute and late toxicity

QoL, quality of life; RT, radiotherapy; HT, hyperthermia; CR, complete response; CCRT, concurrent chemoradiotherapy; OS, overall survival; LR, local recurrence; DM, distant metastasis; TER, total effective rate; OR, odds ratio; GI, gastrointestinal; CT, chemotherapy; RR, relative risk; HR, hazard ratio; LC, local control; LRFs, local relapse-free survival.

Table 2. Summary of oncological outcomes and safety of hyperthermia in randomized controlled trials

Author	Article type	Cancer type	Intervention	Total patients	Endpoints	Oncologic outcomes	Survival outcomes	QoL outcomes	Side effects
Loboda et al. (2020) [37]	Phase II RCT	Breast	NACT+HT vs. NACT	200	Tumor response 10-yr OS	Better tumor size reduction with HT Objective response rate increased by 15.9% ($p=0.034$)	Higher 10-yr OS ($p=0.009$)	-	-
Klimanov et al. (2018) [38]	Phase II RCT	Breast cancer with liver metastases	HT+CT vs. CT alone	103	Tumor response QoL	Higher PR and SD	-	Improved QoL	-
Kang et al. (2013) [40]	Phase II RCT	Head and neck	HT+CCRT vs. CCRT	154	CR DFS OS	Higher 3-mo CR (81.6% vs. 62.8%; $p<0.05$) and 5-yr LC rate (96.1% vs. 76.9%)	Better 5-yr DFS (51.3% vs. 20.5%) and 3-yr (85.5% vs. 61.5%), 5-yr OS (68.4% vs. 50.0%)	-	No statistical difference in toxicity
Zhao et al. (2014) [41]	Phase II RCT	Head and neck	HT+CCRT vs. CCRT	83	OS DFS QoL	-	Higher 3-yr OS (73% vs. 53.9%, $p=0.048$) and PFS (61 mo vs. 38 mo, $p=0.048$)	Better QoL with HT	-
Ren et al. (2021) [42]	Phase II RCT	Head and neck	HT+ induction CT vs. induction CT alone	120	Clinical response rate of induction CT OS DFS Toxicity	Higher clinical response rates (65.45% vs. 40.00%, $p=0.0088$)	Improved DFS (HR, 0.57; $p=0.035$) not OS	-	No difference in adverse events
Dong et al. (2016) [16]	Phase II RCT	Liver	HT+RT vs. RT alone	80	Liver function TER (CR, PR, or SD) Recurrence and mortality rate	Improved liver function and TER (60.0% vs. 47.5%, $p<0.001$)	Lower 1-yr recurrence (27.5% vs. 40.0%, $p<0.001$) and mortality rates (12.5% vs. 20.0%, $p<0.001$)	-	-
Mitsumori et al. (2007) [43]	Phase II RCT	Lung	HT+RT vs. RT alone	80	LRR LPFS OS	No difference in LRR	Better LPFS ($p=0.036$) with HT No difference in OS	-	No grade 3 late toxicity
Shen et al. (2011) [44]	Phase II RCT	Lung	CT+HT vs. CT alone	80	Response rate QoL Toxicity	No difference in response rate	No survival data reported	Improved QoL with HT (82.5% vs. 47.5%, $p<0.05$)	Toxicity was not statistically analyzed
Schulze et al. (2006) [45]	Phase II RCT	Rectum	HT+CCRT vs. CCRT	137	GI QoL index	-	-	No difference in QoL	-

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Table 2. Continued

Author	Article type	Cancer type	Intervention	Total patients	Endpoints	Oncologic outcomes	Survival outcomes	QoL outcomes	Side effects
Issels et al. (2018) [47]	Phase III RCT	Soft tissue sarcoma	HT+NACT vs. NACT alone	341	LPFS OS	-	Improved LPFS (HR, 0.65; $p=0.002$) and OS (HR, 0.73; $p=0.04$) Prolonged 5-yr (62.7% vs. 51.3%) and 10-yr (52.6% vs. 42.7%) survival rate	-	-
Jones et al. (2005) [49]	Phase II RCT	Superficial skin tumor	HT+RT vs. RT alone	108	CR LC OS	Improved CR (OR, 2.7; $p=0.02$)	No OS benefit	-	-
Minnaar et al. (2022) [52]	Phase III RCT	Uterine cervix	HT+CCRT vs. CCRT	210	LC Toxicity QoL 2-yr OS	Better 6-mo LC ($p=0.003$) and 2-yr (HR, 0.67; $p=0.017$) and 3-yr DFS (HR, 0.70; $p=0.035$)	No OS benefit (except for FIGO III)	Better QoL (pain reduction) with HT	No difference in toxicity
Van der Zee et al. (2000) [54]	Phase III RCT	Uterine cervix and bladder	HT+RT vs. RT alone	101	CR LC OS	Bladder: Improved CR (55% vs. 39%, $p=0.001$), not LC Uterine cervix: Improved CR (83% vs. 57%, $p=0.003$)	Bladder: No OS gain Uterine cervix: Improved 3-yr OS (51% vs. 27%, $p=0.009$)	-	No difference in acute and late toxicities
Chi et al. (2018) [55]	Phase III RCT	Painful bone metastases	HT+RT vs. RT alone	108	Pain response Time to pain progression Toxicity	Improved pain response (CR, 37.9% vs. 7.1%, $p=0.006$) Longer time to pain progression (HR, 0.178; $p<0.001$)	-	-	No grade 3 adverse events in both arms

QoL, quality of life; RCT, randomized controlled trial; NACT, neoadjuvant chemotherapy; HT, hyperthermia; OS, overall survival; CT, chemotherapy; PR, partial response; SD, stable disease; CCRT, concurrent chemoradiotherapy; CR, complete response; DFS, disease-free survival; LC, local control; HR, hazard ratio; RT, radiotherapy; TER, total effective rate; LRR, local response rate; LPFS, local progression-free survival; GI, gastrointestinal; OR, odds ratio.

CONCLUSION

Theoretically and experimentally, mEHT can play an important role in treating tumors, either alone or in combination with chemotherapy and radiation therapy. Although several studies have reported the clinical use of mEHT, particularly in improving oncological outcomes, further research is still required on the optimized treatment dose or schedule. In some patients, the effect of

hyperthermia is minimal, so it cannot improve the disease state and may only increase the social and economic burden. Therefore, hyperthermia should be applied with appropriate monitoring in selected patients. Since various treatment methods and regimens are used in the treatment of tumors, we believe that multidisciplinary medical consultations are also useful in determining the treatment plan.

ARTICLE INFORMATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11–20.
2. Schneider BJ, Ismaila N, Altorki N. Lung cancer surveillance after definitive curative-intent therapy: ASCO guideline summary. *JCO Oncol Pract* 2020;16:83–6.
3. Daly ME, Ismaila N, Decker RH, Higgins K, Owen D, Saxena A, et al. Radiation therapy for small-cell lung cancer: ASCO guideline endorsement of an ASTRO guideline. *J Clin Oncol* 2021; 39:931–9.
4. Fiorentini G, Szasz A. Hyperthermia today: electric energy, a new opportunity in cancer treatment. *J Cancer Res Ther* 2006; 2:41–6.
5. Andocs G, Szasz O, Szasz A. Oncothermia treatment of cancer: from the laboratory to clinic. *Electromagn Biol Med* 2009; 28:148–65.
6. Roussakow SV. Clinical and economic evaluation of modulated electrohyperthermia concurrent to dose-dense temozolomide 21/28 days regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-centre German cohort trial with systematic comparison and effect-to-treatment analysis. *BMJ Open* 2017;7:e017387.
7. Kirui DK, Koay EJ, Guo X, Cristini V, Shen H, Ferrari M. Tumor vascular permeabilization using localized mild hyperthermia to improve macromolecule transport. *Nanomedicine* 2014; 10:1487–96.

8. Oei AL, Vriend LE, Krawczyk PM, Horsman MR, Franken NA, Crezee J. Targeting therapy-resistant cancer stem cells by hyperthermia. *Int J Hyperthermia* 2017;33:419–27.
9. Baronzio G, Gramaglia A, Fiorentini G. Hyperthermia and immunity: a brief overview. *In Vivo* 2006;20(6A):689–95.
10. Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, et al. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002;43:33–56.
11. Kang G, Kim SE. How to write an original article in medicine and medical science. *Kosin Med J* 2022;37:96–101.
12. Kim DJ, Kil SY, Son J, Lee HS. How to conduct well-designed clinical research. *Kosin Med J* 2022;37:187–91.
13. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. *Int J Hyperthermia* 2003;19:267–94.
14. Griffin RJ, Dings RP, Jamshidi-Parsian A, Song CW. Mild temperature hyperthermia and radiation therapy: role of tumour vascular thermotolerance and relevant physiological factors. *Int J Hyperthermia* 2010;26:256–63.
15. Datta NR, Ordonez SG, Gaipf US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and/or chemotherapy: recent advances and promises for the future. *Cancer Treat Rev* 2015;41:742–53.
16. Dong Y, Wu G. Analysis of short and long term therapeutic effects of radiofrequency hyperthermia combined with conformal radiotherapy in hepatocellular carcinoma. *J BUON* 2016;21:407–11.
17. Skandalakis GP, Rivera DR, Rizea CD, Bouras A, Jesu Raj JG, Bozec D, et al. Hyperthermia treatment advances for brain tumors. *Int J Hyperthermia* 2020;37:3–19.
18. Moeller BJ, Dewhirst MW. HIF-1 and tumour radiosensitivity. *Br J Cancer* 2006;95:1–5.
19. Kaur P, Hurwitz MD, Krishnan S, Asea A. Combined hyperthermia and radiotherapy for the treatment of cancer. *Cancers (Basel)* 2011;3:3799–823.
20. Lee SY, Kim JH, Han YH, Cho DH. The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma. *Int J Hyperthermia* 2018;34:953–60.
21. Elming PB, Sorensen BS, Oei AL, Franken NA, Crezee J, Overgaard J, et al. Hyperthermia: the optimal treatment to overcome radiation resistant hypoxia. *Cancers (Basel)* 2019;11:60.
22. Schneider CS, Woodworth GF, Vujaskovic Z, Mishra MV. Radiosensitization of high-grade gliomas through induced hyperthermia: review of clinical experience and the potential role of MR-guided focused ultrasound. *Radiother Oncol* 2020;142:43–51.
23. Hegyi G, Szigeti GP, Szasz A. Hyperthermia versus oncothermia: cellular effects in complementary cancer therapy. *Evid Based Complement Alternat Med* 2013;2013:672873.
24. Lee SY, Lee NR, Cho DH, Kim JS. Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. *Oncol Lett* 2017;14:73–8.
25. Gadaleta-Caldarola G, Infusino S, Galise I, Ranieri G, Vinciarelli G, Fazio V, et al. Sorafenib and locoregional deep electro-hyperthermia in advanced hepatocellular carcinoma: a phase II study. *Oncol Lett* 2014;8:1783–7.
26. Wismeth C, Dudel C, Pascher C, Ramm P, Pietsch T, Hirschmann B, et al. Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas: phase I clinical results. *J Neurooncol* 2010;98:395–405.

27. Kouloulis VE, Nikita KS, Kouvaris JR, Uzunoglu NK, Golematis VC, Papavasiliou CG, et al. Cytorreductive surgery combined with intraoperative chemo-hyperthermia and postoperative radiotherapy in the management of advanced pancreatic adenocarcinoma: feasibility aspects and efficacy. *J Hepatobiliary Pancreat Surg* 2001;8:564–70.
28. Herold Z, Szasz AM, Dank M. Evidence based tools to improve efficiency of currently administered oncotherapies for tumors of the hepatopancreatobiliary system. *World J Gastrointest Oncol* 2021;13:1109–20.
29. van der Horst A, Versteijne E, Besselink MG, Daams JG, Bulle EB, Bijlsma MF, et al. The clinical benefit of hyperthermia in pancreatic cancer: a systematic review. *Int J Hyperthermia* 2018;34:969–79.
30. Fiorentini G, Giovanis P, Rossi S, Dentico P, Paola R, Turrisi G, et al. A phase II clinical study on relapsed malignant gliomas treated with electro-hyperthermia. *In Vivo* 2006;20(6A):721–4.
31. Ohguri T, Imada H, Yahara K, Narisada H, Morioka T, Nakano K, et al. Concurrent chemoradiotherapy with gemcitabine plus regional hyperthermia for locally advanced pancreatic carcinoma: initial experience. *Radiat Med* 2008;26:587–96.
32. Bakshandeh-Bath A, Stoltz AS, Homann N, Wagner T, Stolting S, Peters SO. Preclinical and clinical aspects of carboplatin and gemcitabine combined with whole-body hyperthermia for pancreatic adenocarcinoma. *Anticancer Res* 2009;29:3069–77.
33. Yeo SG. Definitive radiotherapy with concurrent oncothermia for stage IIIB non-small-cell lung cancer: a case report. *Exp Ther Med* 2015;10:769–72.
34. Rao W, Deng ZS, Liu J. A review of hyperthermia combined with radiotherapy/chemotherapy on malignant tumors. *Crit Rev Biomed Eng* 2010;38:101–16.
35. Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. *Int J Hyperthermia* 2006;22:191–6.
36. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *In Phys* 2016;94:1073–87.
37. Loboda A, Smolanka I Sr, Orel VE, Syvak L, Golovko T, Dosenko I, et al. Efficacy of combination neoadjuvant chemotherapy and regional inductive moderate hyperthermia in the treatment of patients with locally advanced breast cancer. *Technol Cancer Res Treat* 2020;19:1533033820963599.
38. Klimanov MY, Syvak LA, Orel VE, Lavryk GV, Tarasenko TY, Orel VB, et al. Efficacy of combined regional inductive moderate hyperthermia and chemotherapy in patients with multiple liver metastases from breast cancer. *Technol Cancer Res Treat* 2018;17:1533033818806003.
39. Hu Y, Li Z, Mi DH, Cao N, Zu SW, Wen ZZ, et al. Chemoradiation combined with regional hyperthermia for advanced oesophageal cancer: a systematic review and meta-analysis. *J Clin Pharm Ther* 2017;42:155–64.
40. Kang M, Liu WQ, Qin YT, Wei ZX, Wang RS. Long-term efficacy of microwave hyperthermia combined with chemoradiotherapy in treatment of nasopharyngeal carcinoma with cervical lymph node metastases. *Asian Pac J Cancer Prev* 2013;14:7395–400.
41. Zhao C, Chen J, Yu B, Chen X. Improvement in quality of life in patients with nasopharyngeal carcinoma treated with non-invasive extracorporeal radiofrequency in combination with chemoradiotherapy. *Int J Radiat Biol* 2014;90:853–8.
42. Ren G, Ju H, Wu Y, Song H, Ma X, Ge M, et al. A multicenter randomized phase II trial of hyperthermia combined with TPF induction chemotherapy compared with TPF induction

- chemotherapy in locally advanced resectable oral squamous cell carcinoma. *Int J Hyperthermia* 2021;38:939–47.
43. Mitsumori M, Zeng ZF, Oliynychenko P, Park JH, Choi IB, Tatsuzaki H, et al. Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency. *Int J Clin Oncol* 2007;12:192–8.
 44. Shen H, Li XD, Wu CP, Yin YM, Wang RS, Shu YQ. The regimen of gemcitabine and cisplatin combined with radio frequency hyperthermia for advanced non-small cell lung cancer: a phase II study. *Int J Hyperthermia* 2011;27:27–32.
 45. Schulze T, Wust P, Gellermann J, Hildebrandt B, Riess H, Felix R, et al. Influence of neoadjuvant radiochemotherapy combined with hyperthermia on the quality of life in rectum cancer patients. *Int J Hyperthermia* 2006;22:301–18.
 46. De Haas-Kock DF, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, van Mastrigt GA, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. *Cochrane Database Syst Rev* 2009;(3):CD006269.
 47. Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 Randomized Clinical Trial. *JAMA Oncol* 2018;4:483–92.
 48. Veltsista PD, Oberacker E, Ademaj A, Corradini S, Eckert F, Florcken A, et al. Hyperthermia in the treatment of high-risk soft tissue sarcomas: a systematic review. *Int J Hyperthermia* 2023; 40:2236337.
 49. Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vujaskovic Z, Yu D, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005;23:3079–85.
 50. Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DF, Buijsen J, Mastrigt GA, et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* 2010;2010:CD006377.
 51. Datta NR, Rogers S, Klingbiel D, Gomez S, Puric E, Bodis S. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. *Int J Hyperthermia* 2016; 32:809–21.
 52. Minnaar CA, Maposa I, Kotzen JA, Baeyens A. Effects of modulated electro-hyperthermia (mEHT) on two and three year survival of locally advanced cervical cancer patients. *Cancers (Basel)* 2022;14:656.
 53. Yea JW, Park JW, Oh SA, Park J. Chemoradiotherapy with hyperthermia versus chemoradiotherapy alone in locally advanced cervical cancer: a systematic review and meta-analysis. *Int J Hyperthermia* 2021;38:1333–40.
 54. van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. *Lancet* 2000;355:1119–25.
 55. Chi MS, Yang KL, Chang YC, Ko HL, Lin YH, Huang SC, et al. Comparing the effectiveness of combined external beam radiation and hyperthermia versus external beam radiation alone in treating patients with painful bony metastases: a phase 3 prospective, randomized, controlled trial. *Int J Radiat Oncol Biol Phys* 2018;100:78–87.