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Current understanding of modulated electro-hyperthermia in cancer treatment

Sungmin Kim[1], Jesang Yu[2], Jihun Kang[3], Yunkyung Kim[4], Taek Yong Ko[5]

[1]*Department of Radiation Oncology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea*
[2]*Department of Radiation Oncology, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[3]*Department of Family Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[4]*Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*
[5]*Department of Thoracic and Cardiovascular Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea*

Traditional hyperthermia involves increasing the temperature at the tumor site to above 39 °C, inducing 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 combine 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 mem-

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Corresponding Author: Jesang Yu, MD, PhD
Department of Radiation Oncology, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-6480 Fax: +82-51-990-6852 E-mail: rojsyu@gmail.com

branes 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.

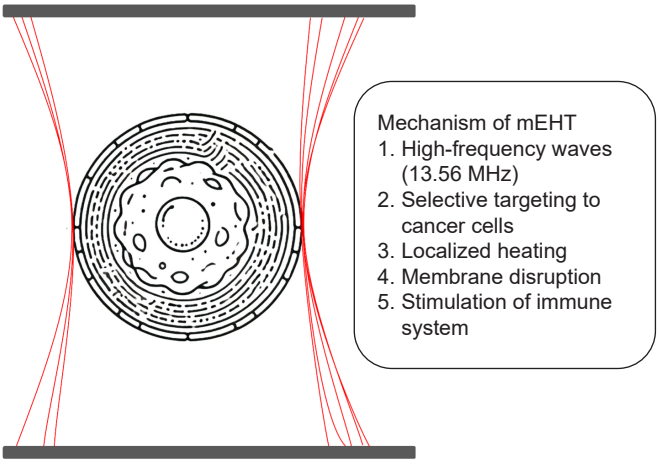

Fig. 1. Mechanism of modulated electro-hyperthermia (mEHT).

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

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; $p=0.05$)	-	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. 53.5%, 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	-

(Continued to the next page)

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.

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.

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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Author contributions

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ORCID

Sungmin Kim, https://orcid.org/0000-0003-0225-500X
Jesang Yu, https://orcid.org/0000-0002-0469-2660
Jihun Kang, https://orcid.org/0000-0002-2263-9054
Yunkyung Kim, https://orcid.org/0000-0003-0393-7264
Taek Yong Ko, https://orcid.org/0000-0002-0096-0664

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