


A Narrative Review of Regional Hyperthermia: Updates From 2010 to 2019

Integrative Cancer Therapies
Volume 19: 1–13
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735420932648
journals.sagepub.com/home/ict


Giammaria Fiorentini, MD^{1,3} , Donatella Sarti, PhD¹,
Cosmo Damiano Gadaleta, MD², Marco Ballerini, MD³, Caterina Fiorentini, MD⁴,
Tommaso Garfagno, MD⁵, Girolamo Ranieri, MD² and Stefano Guadagni, MD⁶

Abstract

The role of hyperthermia (HT) in cancer therapy and palliative care has been discussed for years in the literature. There are plenty of articles that show good feasibility of HT and its efficacy in terms of tumor response and survival improvements. Nevertheless, HT has never gained enough interest among oncologists to become a standard therapy in clinical practice. The main advantage of HT is the enhancement of chemotherapy (CHT), radiotherapy (RT), chemoradiotherapy (CRT), and immunotherapy benefits. This effect has been confirmed in several types of tumors: esophageal, gastrointestinal, pancreas, breast, cervix, head and neck, and bladder cancers, and soft tissue sarcoma. HT effects include oxygenation and perfusion changes, DNA repair inhibition and immune system activation as a consequence of new antigen exposure. The literature shows a wide variety of randomized, nonrandomized, and observational studies and both prospective and retrospective data to confirm the advantage of HT association to CHT and RT. There are still many ongoing trials on this subject. This article summarizes the available literature on HT in order to update the current knowledge on HT use in association with RT and/or CHT from 2010 up to 2019.

Keywords

regional hyperthermia, radiotherapy, chemotherapy, health technology assessment, gastrointestinal tumors, integrative cancer therapy

Submitted December 19, 2019; revised April 30, 2020; accepted May 14, 2020

Introduction

Regional hyperthermia (HT) is defined as an external, supraphysiological increase of tissue/body temperature using external electromagnetic fields with rapid field alternations.¹ HT is currently used for local/locoregional heat application alone or complementary to radiotherapy (RT) and/or chemotherapy (CHT), increasing their efficacy in terms of both tumor response and survival, while keeping toxicity at comparable levels to the single therapies.¹ Another advantage of HT association to RT increases its effects, and in cases of re-irradiation, where standard dose or dose escalation is not possible, HT can augment the radiation treatment.¹

Multimodal therapies involving HT are applied to several types of tumors: colorectal, pancreas, breast, and bladder cancers, and soft tissue sarcoma (STS) with significant clinical benefits.^{1,2}

The complementary application of HT with CHT or RT is successful in several types of tumors such as pancreatic,

brain, and breast cancers.^{3–5} The use of HT to increase the sensitivity of tumor cells to ionizing radiation or chemotherapeutic agents is reported in several clinical trials.^{3–6} HT influences perfusion and oxygenation of tumor tissues resulting in increased blood flow and oxygenation enhancing radiosensitivity of the tumor. HT induces apoptosis and

¹Azienda Ospedaliera “Ospedali Riuniti Marche Nord,” Pesaro, Italy

²Department of Interventional and Integrated Medical Oncology, National Cancer Research Centre, IRCCS Istituto Tumori “Giovanni Paolo II”, Bari, Italy

³Private Clinic Ravenna33, Ravenna, Italy

⁴University of Siena, Siena, Toscana, Italy

⁵Department of Radiotherapy University Hospital Siena, Italy

⁶University of L’Aquila, L’Aquila, Italy

Corresponding Author:

Giammaria Fiorentini, Onco-Ematology Department, Azienda Ospedaliera “Ospedali Riuniti Marche Nord”, Via Lombroso 1, Pesaro 61122, Italy.

Email: g.fiorentini@alice.it



Table 1. Esophageal Cancer.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Nishimura et al ¹¹	ND	Esophageal squamous cell carcinoma	11	HT-CRT	27% CR 45% SD	Overall survival rates at 1, 2, and 5 years after CRT were 72.7%, 54.5%, and 9.1%, respectively	ND
Sheng et al ¹²	Respective, observational	Metastatic esophageal squamous cell carcinoma	50	HT-CRT	ND	3-year PFS rate and OS rate were 34.9% and 42.5%, respectively	HT-related pain (38.0%) and fatigue (40.0%). GI-G2

Abbreviations: HT, hyperthermia; ND, not reported; CRT, chemoradiotherapy; CR, complete response; SD, stable disease; PFS, progression-free survival; OS, overall survival; G, grade.

inhibits DNA repair. HT enhances the effects of immunotherapy and induces immune stimulation.

The present article is a literature-based review, based on a search in the PubMed, MEDLINE, Embase, Cochrane, and ClinicalTrials.gov databases of the term “hyperthermia” in combination with CHT and RT in gastrointestinal, esophageal, pancreas, colorectal, breast, cervical, head and neck, and bladder cancers, and soft tissue sarcoma lesions. This review aims to update the current knowledge on HT use in association with RT and/or CHT from 2010 up to 2019.

Heating techniques are classified according to the size, penetration depth, and region of energy release. Local or regional HT is generally associated with RT or CHT. Whole-body HT can be performed alone or in combination with CHT in cases of metastatic cancer. Different methods are used for HT: capacitive, radiative, infrared-A, or ultrasound are among the most used techniques.¹

Capacitive local heating requires the positioning of 2 electrodes on both sites of the body with direct body contact using a water bolus, and the heat is obtained by the electric current flow between the 2 electrodes.¹ Radiative heating uses frequencies of 75 to 915 MHz and a water bolus for electromagnetic coupling.¹ This method allows obtaining a better temperature distribution leading to homogeneous target coverage by heat than capacitive coupling. Walter-filtered infrared-A-based HT is used for superficial tumors (15-20 mm depth), using a halogen lamp, passing through a water filter.¹

Modulated electro-hyperthermia (mEHT) is a type of HT that can be performed using the EHY-2000+ device (OncoTherm Ltd). It is a safe form of HT, resulting only in mild adverse events, such as skin burn or pain, and heat-related injuries are observed in 5% of cases.⁶ mEHT has comparable benefits as those obtained with other types of HT, improving local control and survival rates in several types of tumors, such as cervical, brain, and pancreatic cancer.⁶ mEHT targets the malignant cells selectively, heating and sensitizing them to subsequent oncological therapies (CHT and/or RT). A

recent review of mEHT effects in different types of cancer shows promising results concerning both local disease control and survival.⁶

Methods

The article search was performed using the following terms: regional hyperthermia, efficacy, toxicity, in PubMed, MEDLINE, Embase, Cochrane, and ClinicalTrials.gov databases. The search retrieved 1662 articles. A further selection was made to include only observational or experimental trial that were published from 2010 through December 2019 without language limitation. Review articles were discarded from tables and were used for the introduction and general considerations. This review included 42 articles that were divided according to tumor type. Efficacy and toxicity of HT were described for each tumor type separately.

Esophageal Cancer

Phase II trials report the feasibility of chemoradiotherapy (CRT) + HT as neoadjuvant treatment.⁷⁻¹⁰ A study on esophageal squamous cell carcinoma treated with CRT + HT shows 27% of complete response (CR) and 45% of stable disease (SD) with overall survival rates at 1, 2, and 5 years after CRT of 72.7%, 54.5%, and 9.1%, respectively (Table 1).¹¹ The data from a retrospective study on metastatic esophageal squamous cell carcinoma report that 3-year progression-free survival (PFS) rate and overall survival (OS) rate were 34.9% and 42.5%, respectively, after CRT + HT therapy, and HT-related pain (38.0%) and fatigue (40.0%) were of mild intensity, grade (G) 1 to 2 (Table 1).¹¹

The available literature reports evidence of CRT + HT benefits in esophageal cancer therapy; nevertheless, further randomized clinical trials are required to compare CRT + HT versus CRT alone to confirm the above-mentioned data.

Table 2. Colorectal Cancer.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Ott et al ²¹		Squamous rectal cancer	112	CRT vs CRT + HT		5-year follow-up, overall (95.8% vs 74.5%, $P = .045$), disease-free (89.1% vs 70.4%, $P = .027$), local recurrence-free (97.7% vs 78.7%, $P = .006$), and colostomy-free survival rates (87.7% vs 69.0%, $P = .016$)	Comparable toxicity: skin reaction, diarrhea, stomatitis, and nausea/emesis were not increased with the additional use of HT.
Zwirner et al ¹⁵	Nonrandomized prospective study	Locally advanced rectal cancer	86	Preoperative CRT + HT		5-year OS = 87.3%, DFS = 79.9%, and LRFS = 95.8%, respectively	ND
Gani et al ¹⁴	Nonrandomized retrospective study	Adenocarcinoma of the middle or lower rectum	103	Neoadjuvant 43 CRT 60 CRT + HT		5-year CRT: OS = 76%, DFS = 73%, and LRFS = 77%, 5-year CRT - HT: OS = 88% ($P < .08$), DFS = 78%, and LRFS = 75%, respectively	ND
Shoji et al ¹⁶	Nonrandomized prospective study	Rectal cancer	49	Preoperative CRT + HT	CR + pCR = 29%		One case of G3 perianal dermatitis
Kato et al ¹⁸	Nonrandomized prospective study	Locally advanced rectal cancer	48	Preoperative CRT - HT	pCR = 69%		No hematological toxicity
Schroeder et al ¹⁹	Nonrandomized prospective study	Locally advanced rectal cancer	106	Neoadjuvant 45 CRT vs 61 CRT + HT	pCR rate: CRT + HT = 22.5% ($P = .043$)		ND
Maluta et al ¹⁷	Nonrandomized prospective study	Locally advanced adenocarcinoma of middle and lower rectum	76	Preoperative CRT - HT	CR = 23.6% Disease control = 94.8%	5-year OS = 86.5%, DFS = 74.5%, and LRFS = 73.2%, respectively	G0-G2 general or local discomfort in 15%, no G3, G4 subcutaneous burns in 5.2%

Abbreviations: HT, hyperthermia; CRT, chemoradiotherapy; OS, overall survival; DFS, disease-free survival; LRFS, local relapse-free survival; ND, not specified; CR, complete response; G, grade; pCR, pathologic complete response.

Colorectal Cancer

Surgery is the standard treatment for patients with colorectal cancer; however, the results are very poor for locally advanced cancer, in terms of both survival and recurrence.¹³ The main aim of the treatments for locally advanced rectal cancer is the achievement of high resectability; for this reason, neoadjuvant CRT is often used to obtain high percentages of pathologic CR (pCR).¹⁴

The introduction of CRT improves locoregional control for locally advanced colorectal cancer. This improvement is further achieved when CRT is associated to HT, resulting in long-term tumor control and survival in locally advanced nonmetastatic rectal cancer.¹⁵ CRT + HT allows achievement of promising rates of pCR, ranging from 22.5% to 69% (Table 2). This association is safe, showing comparable toxicity with CRT alone and 6.5% of G >3 adverse events, such as skin reaction, diarrhea, stomatitis, and nausea/emesis, which were not increased with the additional

use of HT; moreover, subcutaneous burns in 5.2% disappeared spontaneously within 2 weeks.¹⁶⁻²¹ Other HT-related adverse events were of G0 to G2 and included general or local discomfort in 15% of cases.¹⁷ Concerning survival, CRT + HT allows longer OS with 5-year OS significantly higher than CRT alone (88% vs 76% $P < .08$).¹⁶

RT + HT is effective and well tolerated also in chemorefractory liver metastases from colorectal cancer, resulting in mild/moderate toxicity and the objective response of 30%.²⁰

In conclusion, preoperative CRT and HT association yields to acceptable toxicity, improved response rate, and survival; however, further studies are required to confirm the long-term benefit of CRT + HT in locally advanced colorectal cancer and liver metastases.

Pancreatic Cancer

The incidence of pancreatic cancer is constantly increasing, and pancreatic cancer reaches the fourth place among the

Table 3. Pancreas.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Fiorentini et al ²⁴	Retrospective multicentric study	Advanced pancreatic cancer	106	mEHT + RT or CHT vs RT or CHT (no-mEHT)	mEHT vs no-mEHT DC = 92% vs 66%	mEHT vs no-mEHT OS = 18.0 vs 10.9 months	No grade III-IV toxicity
Tschoep-Lechner et al ²⁵	Retrospective study	Advanced pancreatic cancer	27	CHT + HT	DC = 50%	PFS = 5.9 months OS = 12.9 months	No grade III-IV toxicity
Maluta et al ²⁶	Prospective, nonrandomized controlled study	Locally advanced unresectable pancreatic cancer	68	CRT CRT + HT		CRT + HT median OS = 15 vs 11 months	
Volovat et al ³⁰	Prospective study	Locally advanced pancreatic cancer	26	CHT + HT	DC = 71%	Median PFS = 3.9 months Median OS = 8.9 months	No grade III-IV toxicity
Ohguri et al ²⁸	Retrospective study	Locally advanced pancreatic cancer	29	CRT + HT CRT		Median OS = 8.8 vs 4.9 months, <i>P</i> = .02 Median PFS = 18.6 vs 9.6 months, <i>P</i> = .01	5% grade III-IV toxicity

Abbreviations: HT, hyperthermia; mEHT, modulated electro-HT; RT, radiotherapy; CHT, chemotherapy; DC, disease control; OS, overall survival; PFS, progression-free survival; CRT, chemoradiotherapy.

most frequent causes of cancer deaths.²² Advanced unresectable pancreatic cancer is diagnosed in >80% of patients, and standard first-line treatment is still missing for this population that develops recurrence in an average of 6 months with a very low OS of 1.9 months. Gemcitabine-based CHT is the most common treatment for unresectable pancreatic cancer, whereas FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) is more indicated for fit patients because of the high toxicity.²³ mEHT is feasible for both palliative care and therapeutic purposes also in advanced pancreatic cancer,²⁴⁻³⁰ increasing OS and improving quality of life. These advantages of mEHT and HT are observed when it is used alone or in association with CRT for locally advanced pancreas carcinoma.²⁴⁻³⁰ Median OS increases from 10% to 11% of CRT alone to 15% to 18% of CRT + HT (Table 3). The disease control (DC) rate increases from 66% to 92% after mEHT.²⁴ Regional HT also shows encouraging DC rate (50%). As concerning the safety, no grade III to IV toxicity is observed, suggesting the good tolerability of HT in pancreatic cancer treatment.

Further studies that will investigate the effects of HT include the HEATPAC trial, a phase II randomized trial, in unresectable locally advanced pancreatic cancer that will explore the feasibility and efficacy of HT associated with CRT versus CRT alone, with pre- and postintervention FOLFIRINOX.²⁹

In conclusion, longer median OS and better tumor response can be obtained in correlation with HT treatment, suggesting a beneficial effect of HT in association with CHT and/or in locally advanced or metastatic pancreatic cancer with a low toxicity profile.

Breast Cancer

As concerning breast cancer therapy, surgery and CRT are very effective; however, there is a 30% local recurrence.^{1,2}

HT is among the oldest methods of cancer therapy, and since 2013, it has been included in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for the treatment of recurrent breast cancer.^{31,32} HT increases the temperature of the tumor up to 42 °C to 45 °C using different methods, inducing tumor death. HT is often used in association with CHT or RT and immunotherapy, increasing their efficacy and prolonging their clinical benefits.^{5,33-35}

This beneficial effect is due to heat-induced improvement of CHT delivery, increase of blood flow, and oxygen radical production, while inhibiting hypoxia, angiogenesis, and DNA repair, resulting in enhanced apoptosis of tumor cells.^{5,33,34}

The analysis of the literature shows 9 clinical trials (Table 4) on advanced or recurrent breast cancer treatment with HT combined therapy from 2010 up to 2019.³⁶⁻⁴⁴ The association of HT to RT resulted in CR in a range of 52.7% to 76% with local control rates of 53% to 76% at 1 year, 25% to 78% at 3 years, and 39% to 65% at 5 years.³⁶⁻⁴⁴

Five studies report the results of survival analysis and show survival rates of 58.3% to 75% at 1 year, 29.5% to 66% at 3 years, 18% to 36% at 5 years, and one study showed also a 10% survival at 10 years.⁴¹

As concerning the toxicity, adverse events (>G3 intensity, according to CTCAE [Common Terminology Criteria for Adverse Events] criteria) are observed in a small portion of patients (10% to 31%) and include thermal burns, ulceration, and osteoradionecrosis.³⁶⁻⁴¹

The combination of re-irradiation and HT results in high tumor response and local control rates that are maintained for up to 10 years in advanced or recurrent breast cancer. This combination, moreover, offers long survival and is well tolerated. For this reason, this combined treatment should be suggested to all patients with advanced or recurrent or at high risk of local recurrence.

Table 4. Breast Cancer.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
De-Colle et al ⁴²	Prospective observational study	Recurrent breast cancer	20	RT + HT	Clinical benefit = 90%	2 years: OS = 90% and DFS = 90% 5 years: OS = 50%	>G3 toxicity in 15%
Klimanov et al ³⁷		Metastatic breast cancer	103	53 CHT + HT 50 CHT	Clinical benefit = 76% (CHT + HT) vs 42% (CHT), $P < .05$		
Linthorst et al ³⁹		Recurrent breast cancer	248	RT + HT	CR rate 70% 1-, 3-, and 5-year LC was 53%, 40%, and 39%, respectively	SR at 1, 3, and 5 years = 66%, 32%, and 18%, respectively	
Oldenberg et al ⁴⁰		Recurrent breast cancer	404	RT + HT	CR = 86% ORR was 86%. 3-year LC rate was 25%	Median = 17 months and SR at 3 year = 37%	>G3 toxicity in 24%
Refaat et al ⁴³		Recurrent or advanced breast cancer	127	RT + HT	CR = 52.7% LC = 55.1%	SR at 1, 3, and 5 years = 58.3%, 29.5%, and 22.5%, respectively	
Linthorst et al ⁴¹		Recurrent breast cancer	198	RT + HT		Median = 82 months SR at 3, 5, and 10 years = 75%, 60%, and 36%, respectively	G3-G4 toxicity in 10%
Takeda et al ³⁶		Recurrent or advanced breast cancer	172	Immunotherapy + HT	Clinical benefit = 17.6% effective rate of immunotherapy increased from 7.7% to 26.0% using HT		
Varma et al ⁴⁴		Advanced breast carcinoma	59	RT + HT	LC = 70%		>G3 toxicity in 14%
Oldenberg et al ³⁸		Recurrent breast cancer	78	RT + HT	3- and 5-year LC rates were 78% and 65%	3-year survival 66%	G3 toxicity in 32%

Abbreviations: HT, hyperthermia; RT, radiotherapy; clinical benefit, complete response + partial response + stable disease; OS, overall survival; DFS, disease-free survival; G, grade; CHT, chemotherapy; CR, complete response; SR, survival rate; ORR, overall response rate; LC, local control.

The HT in association with CHT is compared with CHT treatment alone in one study.³⁷ This combination improves the therapeutic efficacy in patients with metastatic breast cancer, resulting in a clinical benefit of 76% versus 42% of CHT alone ($P < .05$).³⁷

These data confirm the safety and efficacy of the combination therapy HT/CHT and RT for advanced or recurrent breast cancer in both tumor response and survival; these trials, however, are nonrandomized.³⁶⁻⁴⁴

Cervical Cancer

Concomitant cisplatin-based CHT and RT (CRT) improve OS of locally advanced cervical cancer more than RT alone as reported by a review⁴⁵ and clinical trials,⁴⁶⁻⁴⁸ even if the prognosis is still poor.⁴⁸ HT improves tumor response of CHT-RT in locally advanced cervical cancer.⁴⁷⁻⁵² Several randomized reports HT benefit for locally advanced cervical cancer suggest, including survival improvement and good tolerability (Table 5).⁴⁷⁻⁵²

All recent studies on CRT and CRT-HT reported possible advantages of HT and mEHT association to CRT.^{46,47,49-52,53}

Two of them show better 5-year OS, disease-free survival (DFS), and local relapse-free survival (LRFS) in the CRT-HT group than those in the CRT group^{47,49}; however, the difference is not statistically significant. CR is significantly higher in the CRT-HT group than that in the CRT group. As concerning safety, the addition of HT is well tolerated, and no additional acute or long-term toxicity is observed than CRT alone.^{47,49}

One of the above-mentioned studies measures the intrarectal temperature with a 4-point micro-thermocouple sensor during regional whole-pelvis HT of locally advanced cervical cancer patients associated to CRT.⁴⁷ It shows that higher thermal dose parameter of HT significantly increases LRFS in both univariate ($P = .024$) and multivariate ($P = .0097$) analyses.⁴⁷ The same result is observed for DFS ($P = .071$) and tumor response ($P = .056$). DFS, LRFS, and CR are significantly improved after CRT-HT at higher temperature than CRT alone ($P = .036$, $P = .036$, and $P = .048$).⁴⁷

Table 5. Cervical Cancer.

Reference	Type of study	FIGO stage	n	Treatment	Tumor response	Survival	HT-associated adverse events
Minaar et al ⁵²	Single-center, phase III, randomized controlled, parallel-group study trial	IIB to IIIB	202	101 CRT-mEHT 101 CRT	CRT-mEHT group: CR = 45.5% CRT group: CR = 24.1%	CRT-mEHT group: 6-month DFS = 87.1% CRT group: 6-month DFS = 82.2% 5-year OS = 65%, DFS = 73%, and LRFS = 81%, respectively	10.6% mEHT related: GI-G2 adipose tissue burns (9.5%); GI surface burns (2.0%) >G3 toxicity none related to HT
Ohguri et al ⁴⁷	Prospective, multicentric, randomized, parallel-group study	IB bulky (>4 cm), IIA, IIB, IIIA, IIIB, or IVA	47	CRT-HT	CR = 87%		
Harima et al ⁴⁹	Prospective, multicentric, randomized, parallel-group study conducted	IB bulky (>4 cm), IIA, IIB, IIIA, IIIB or IVA	101	CRT-HT CRT	CRT-HT group: CR = 88% CRT group: CR = 77.6%	CRT-HT group: 5-year OS = 77.8%, DFS = 70.8%, and LRFS = 80.1% CRT group: 5-year OS = 64.8%, DFS = 60.6%, and LRFS = 71.0%	CRT-HT was well tolerated and caused no additional acute or long-term toxicity compared with CRT alone
Lurgens et al ⁴⁶	Phase III randomized	FIGO stage IIIB, IVA,	87	43 RT + CHT 44 RT + HT		DFS: HR = 1.15, ns OS: HR = 1.04, ns LRFS: HR = 0.94, ns Median DFS = 15 months OS 23% at 12 months and 4% at 24 months	>G3 = 10%
Heijkoop et al ⁵⁰	Prospective nonrandomized	All FIGO	43	CRT + HT	Clinical benefit = 49%		
Westermann et al ⁵¹	Prospective phase I-II studies, multicentric	FIGO stage IIB, IVA, unresectable IB	68	CRT-HT	Clinical benefit = 59%		No
Heijkoop et al ⁵³	Single-center, prospective nonrandomized	FIGO stage IB2, IIB, IIIB, IIIA, IVA	43	Neoadjuvant CHT + RT + HT	Response rate = 81.4%	1-year OS = 79% 5-year RFS = 57.5%, OS = 66.1%	>G3 toxicity = 10%

Abbreviations: HT, hyperthermia; CRT, chemoradiotherapy; mEHT, modulated electro-RT; CR, complete response; DFS, disease-free survival; G, grade; OS, overall survival; LRFS, local relapse-free survival; clinical benefit, complete response + partial response + stable disease; RT, radiotherapy; HR, hazard ratio; ns, not significant; CHT, chemotherapy.

Table 6. Bladder.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Datta et al ⁵⁷	Prospective, nonrandomized	Muscle invasive bladder cancer	16	RT + HT	Local control rate = 93.7%; distant control rate = 31.3%	5-year OS = 67.5%, DFS = 51.6%, and LRSF = 64.3%, respectively	No >G3 toxicity
Geijsen et al ⁵⁹	Phase I/II, prospective, nonrandomized	Nonmuscle invasive bladder cancer	18	Intravesical mitomycin C-HT	CR = 23%; PR = 15%	2-year DFS = 78%	G1 = 43%, G2 = 14%, no >G3 toxicity
Inman et al ⁵⁸	Prospective, nonrandomized	Nonmuscle invasive bladder cancer	15	Intravesical mitomycin C-HT		3-year DFS = 33%	No >G3 toxicity

Abbreviations: HT, hyperthermia; RT, radiotherapy; OS, overall survival; DFS, disease-free survival; LRSF, local relapse-free survival; G, grade; CR, complete response; PR, partial response.

These data suggest a dose-effect correlation between thermal dose parameters and clinical outcomes in locally advanced cervical cancer patients.⁴⁷ This correlation is confirmed also in another previous study on 420 patients.⁵⁴

The latter study on CRT-HT differentiates the analysis according to nationality and reports 5-year RFS rates of 65.8% for the Dutch patients, 57.4% for Norwegian, and 38.5% for US patients. However, the difference in RFS is significant only between the Netherlands and the United States ($P < .01$, hazard ratio [HR] = 3.096, 95% confidence interval [CI] = 1.2495-7.671).⁵¹ This may suggest a correlation of HT response to patient characteristics of different countries.

A further study reports the results of CRT associated with mEHT compared with CRT alone for the treatment of FIGO stages IIB to IIIB locally advanced cervical cancer.⁵² It reports a higher tumor response for the CRT- mEHT group, CR = 45.5% versus 24.1% of the CRT-alone group (Pearson's χ^2 : $P = .003$) and an improvement in quality of life, in particular as concerning the social functioning ($P = .049$) and emotional functioning ($P = .017$) seen in the mEHT group.⁵² This difference was observed in both HIV-positive and HIV-negative women.⁵² The HT is not associated with an increased toxicity or RT delays and shows reduced posttreatment fatigue and pain at 3 months after therapy.⁴⁹

Bladder Cancer

The beneficial effects of HT associated with CHT or RT have been shown also for bladder cancer (Table 6).^{53,55-57} The induction of regional HT in bladder cancer can be attained with 3 different techniques: 70 to 120 MHz antennas, intracavitary radiofrequency HT using a 916 MHz antenna, and intravesical conductive therapy using a heated perfusate.⁵⁶ The use of 70 MHz had higher recurrence-free survival rate than the use of heated perfusate (78% vs 33%).⁵⁶

Intravesical mitomycin C associated with HT (70 MHz) at mean temperatures of 40.6 °C to 41.6 °C was reported in 2 studies that treated intermediate-/high-risk nonmuscle invasive bladder cancer. The first study showed a CR in 23% and partial response in 15%, and 2-year recurrence-free survival rate was 78%.⁵⁸ As concerning the toxicity, adverse event intensity was G1 in 43% of cases and G2 in 14%.⁵⁸ The second study showed a 3-year recurrence-free survival rate of 33%.⁵⁹ These data suggested that the treatment with mitomycin C and HT in patients with intermediate-/high-risk nonmuscle invasive bladder cancer was effective and safe.^{58,59}

Soft Tissue Sarcoma

Soft tissue sarcoma includes a wide and heterogeneous group of tumors that are derived from connective tissues. Most patients (>80%) present a high-grade histologic type at diagnosis.⁵⁵ STS treatment involves a combination of CHT, RT, and resection.⁶⁰ In this scenario, regional HT is used to improve CHT and RT efficacy, in terms of PFS, DFS, and tumor response (Table 7).⁶¹ CHT-HT significantly improves local PFS (56% vs 45%, $P = .044$) and DFS (56% vs 45%, $P = 0.044$) at 5 years with regard to CHT alone, whereas OS and toxicity do not change significantly between groups.⁶¹ These results suggest an important role of HT in association with CHT for the treatment of abdominal and retroperitoneal high-risk sarcomas after radical surgery.⁶¹

Hyperthermia has a potential role also in association with neoadjuvant CHT for STS, increasing survival, tumor response, and local PFS.^{60,62-64} A phase III randomized study shows a 27% OS improvement as a consequence of neoadjuvant CHT + HT versus neoadjuvant CHT alone.⁶⁴ Neoadjuvant CHT + HT, in particular, results in a statistically significant improvement of 11.4% and 9.9% in the 5-year and 10-year survival rate, respectively (62.7% vs 51.3% and 52.6% vs 42.7%).⁶⁴

Table 7. Soft Tissue Sarcoma.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Issels et al ⁶²	Randomized phase 3 multicentric study	Soft tissue sarcoma	329	Neoadjuvant 162 CHT-HT 167 CHT	Response rate CHT-HT = 38% CHT = 29%	CHT-HT group: OS median = 15.4 years (P = .04), 5-year OS = 62.7%, 10-year OS = 51.3% CHT group: OS median = 6.2 years, 5-year OS = 52.6%, 10-year OS = 42.7%	HT-related adverse events were G1 and G2: pain, bolus pressure, and skin burn
Fendler et al ⁶⁰	Retrospective observational	Soft tissue sarcoma	66	Neoadjuvant CHT-HT	Response rate = 60%	OS median = 22.2 months	
Angele et al ⁶¹	Randomized phase-III multicenter study	Soft tissue sarcoma	149	73 CHT-HT 66 CHT	Soft tissue sarcoma CHT-HT = 34.7% vs CHT = 15.6%	CHT-HT group: 5-year OS = 57%, DFS = 34% (P = .04), and LRFS = 56% (P = .044) CHT group: 5-year OS = 55%, DFS = 27%, and LRFS = 45%	
Schlemmer et al ⁶³	Phase II, nonrandomized	High-risk soft tissue sarcoma	47	Neoadjuvant HT + surgery + CHT + RT	Soft tissue sarcoma = 21%	Median OS = 105 months 5-year OS = 57%, DFS = 55%, and LRFS = 48%	

Abbreviations: HT, hyperthermia; CHT, chemotherapy; OS, overall survival; G, grade; DFS, disease-free survival; LRFS, local relapse-free survival.

Brain Tumors

Glioblastoma multiforme (GBM) is an aggressive brain tumor, representing 45% to 54% of gliomas.^{65,66} GBM prognosis is still poor, notwithstanding the advances in brain tumor treatment, and median OS ranges between 15 and 18 months.⁶⁶ Actually, a standard therapy for recurrent GBM is not yet available; however, emerging results show an advantage of mEHT as an integrative therapy for treatment and not only palliative care of recurrent GBM and astrocytomas (AST; Table 8).⁶⁷⁻⁷³

Available data report a tumor response rate of 24% to 29% for GBM and 43% to 48% for AST 3 months after mEHT, whereas it is 4% for GBM and 10% to 37% for AST in control group.^{69,70} HT also improves the survival of GBM and AST with a median OS of 12 months (range = 5-108) for GBM, and 17 months for AST. Five-year OS is 83% for AST after mEHT versus 25% after best supportive care and 3.5% for GBM after HT versus 1.2% after best supportive care for GBM.⁶⁸ HT also has a low toxicity profile, resulting in no G3 and G4 adverse events.

In conclusion, mEHT may have a beneficial effect on both the treatment and palliation of relapsed GBM and AST in integrative cancer therapy.

Head and Neck Tumors

Radiotherapy + HT is also used in the treatment of head and neck carcinomas, resulting in better CR than RT alone (62.5%

vs 39.6%) with comparable toxicity also (Table 9).⁷⁴ As concerning nasopharyngeal carcinomas, 3 studies report improved CR, PFS, DFS, and OS for CRT + HT treatment.⁷⁵⁻⁷⁷ This response is temperature-dependent; indeed, patients treated with higher temperatures have a better outcome.⁷⁵ In these studies, no difference in toxicity is observed; moreover, patients receiving HT reported a better quality of life after the treatment.⁷⁷ Also, re-irradiations combined with HT result in promising tumor response (CR = 46%).⁷⁸ These data suggest that the association of HT to CRT is a safe and effective choice of therapy for head and neck tumors. For this reason, HT may be suggested for the treatment of elderly or poorly fit patients to spare the toxicity of more aggressive therapies.

Discussion

The available literature includes both retrospective and prospective studies on the benefits of HT association to RT or CRT in several types of tumors, resulting in confirmation of efficacy for the majority of them.¹ These data, however, do not bring the HT to the level of the standard care in many countries. This may be due to different issues, such as reimbursement, technical difficulties and poor proofs of homogenous heating, difficulties in temperature measurements, and a low number of centers performing HT around the world.

There is a need for standardized protocols to be applied in a single tumor type to avoid the current heterogeneity of HT treatments that creates difficulties in comparing the

Table 8. Brain Tumors.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT-associated adverse events
Fiorentini et al ⁷⁰	Retrospective observational 2-arm comparative, multicentric study	Recurrent GBM and AST	164: 114 GBM and 50 AST	mEHT: 29 GBM and 28 AST BSC: 85 GBM and 32 AST	DC mEHT vs BSC: GBM = 62% vs 24% AST = 77% vs 69% P < .05	Median mEHT OS: GBM = 12 months and AST = 17 months	No grade III-IV toxicity
Fiorentini et al ⁶⁹	Retrospective observational 2-arm comparative, multicentric study	Recurrent GBM and AST	149: 111 GBM and 38 AST	mEHT: 28 GBM and 24 AST BSC: 83 GBM and 14 AST	DC mEHT vs BSC: GBM = 54% vs 19% AST = 72% vs 37% P < .05	Median mEHT OS: GBM = 14 months and AST = 16.5 months 1-year OS HT: AST = 77.3% and GBM = 61% 2-year OS HT: AST = 40.9% and GBM = 29% 5-year OS HT vs BSC: AST = 83% vs 25% and GBM = 3.5% vs 1.2%	No grade III-IV toxicity
Roussakow et al ⁶⁸	Prospective cohort study	Recurrent GBM	54	TMZ + mEHT		Median OS = 10.10 months	No grade III-IV toxicity
Fiorentini et al ⁷²	Retrospective study	Recurrent GBM and AST	24	mEHT	DC = 62% The median duration of response = 16 months	Median OS = 19.5 months 1-year OS = 55% 2-year OS = 15%	No grade III-IV toxicity
Heo et al ⁷¹	Cohort study	Recurrent GBM	20	RT + HT		Median OS = 8.4 months 6-month OS = 67% 1-year OS = 30% median PFS = 4.1 months	No grade III-IV toxicity
Wismeth et al ⁷³	Phase I study	Recurrent GBM	15	CHT + HT			No grade III-IV toxicity

Abbreviations: HT, hyperthermia; GBM, glioblastoma multiforme; AST, astrocytomas; mEHT, modulated electro-HT; BSC, best supportive care; DC, disease control; OS, overall survival; TMZ = temozolomide; PFS, progression-free survival; RT, radiotherapy; CHT, chemotherapy.

results of different studies. The frequency of HT treatments reviewed varied from once a week to daily and the mean temperature obtained in each treatment varied widely in the range 39 °C to 43 °C. The use of HT at higher temperatures or applied frequencies is correlated with better outcome,^{47,54} further underlying the need to establish standardized protocols for HT treatments and larger randomized studies on HT variables.

Modulated electro-HT is a modification of conventional HT that targets tumor cell membranes to increase the temperature inside cancer tissue and sensitize it to cancer therapies: RT, CHT, and immunotherapy.⁶ Combination therapies of mEHT and CHT or RT are reported by preclinical and clinical studies.^{6,24,52,68-70} mEHT induces moderate rises in tissue temperatures, improving tumor perfusion, increasing drug absorption and sensitivity to radiation therapy. mEHT is safely used in several types of cancers, such as cervical, brain, and pancreatic tumors, improving local control and survival rates and seems to induce an abscopal (systemic) response to ionizing radiation.^{24,52,68-70}

Applying of HT alone or complementary to other treatments (CHT and/or RT) is assessed in terms of efficacy and tolerability for several types of tumors: esophageal, colorectal, pancreatic, breast, cervix, bladder, and brain tumors, and STS. The data presented confirm the benefits of HT, such as increased tumor response rates, local and distant control rates, and survival in each type of cancer examined. HT was also well tolerated, resulting in a low number and

intensity (G1-G2 mainly) adverse events. No cardiac toxicity is reported in any observed study.

CRT + HT, when compared with CRT alone, improves both OS and DC in esophageal cancer with low toxicity.¹⁰⁻¹² HT is often used in association with preoperative and neoadjuvant CRT also in locally advanced both nonmetastatic and metastatic colorectal cancer, improving OS and long-term tumor control, resulting in mild toxicity, comparable to that or CRT alone.^{14,15,20} The same advantages are observed for advanced pancreatic cancer. HT alone or complementary to CRT is, indeed, feasible for both palliative care and therapeutic purposes, increasing OS and improving quality of life for locally advanced pancreas carcinoma.⁷⁰⁻⁷³

This HTA reports the available literature to show that there is wide evidence that HT associated with CHT, RT, and immunotherapy for advanced or recurrent breast cancer brings about improvements in both tumor response and OS that are maintained for a long time (up to 10 years).³⁶⁻⁴⁴

Successful use of HT is also shown for cervical cancer, improving tumor response rates and quality of life in both social and emotional functioning.⁵² It is observed, moreover, that there is a dose-effect correlation between thermal dose parameters and clinical outcomes and that HT response may be modified by patient characteristics in different countries.^{47,51,54}

Fewer studies are available on the use of HT for bladder cancer treatment. Their data, nevertheless, confirm the

Table 9. Head and Neck.

Reference	Type of study	Site	n	Treatment	Tumor Response	Survival	HT-associated adverse events
Zhao et al ⁷⁷	Phase III randomized, prospective	Nasopharyngeal cancer	83	40 CRT 43 CRT + HT		3 years: OS = 53.5% (CRT) vs 73% (CRT + HT), $P = .041$ PFS = 37.5 (CRT) vs 48 (CRT + HT) months, $P = .05$	
Kang et al ⁷⁵	Phase III randomized, prospective	Nasopharyngeal cancer	154	78 CRT 76 CRT + HT	CR: 62.8% (CRT) vs 81.6% (CRT + HT)	5 years: DFS = 25.5% (CRT) vs 51.3% (CRT + HT), $P < .005$ OS = 50% (CRT) vs 68.4% (CRT + HT), $P < .005$	
Hua et al ⁷⁶	Phase III randomized, prospective	Nasopharyngeal cancer	180	90 CRT 90 CRT + HT	CR: 81.1% (CRT) vs 95.6% (CRT + HT)	5 years: DFS = 63.1% (CRT) vs 72.7% (CRT + HT), $P < .005$ OS = 70.3% (CRT) vs 78.2% (CRT + HT), ns	

Abbreviations: HT, hyperthermia; CRT, chemoradiotherapy; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; ns, not significant.

positive effects of HT associated with intravesical mitomycin C in terms of CR and PFS in bladder cancer.⁵⁷⁻⁵⁹

As concerning STS, the association of HT with RT or CHT improves local PFS and DFS after radical surgery.⁶¹ The same benefits are observed when HT is used in the neoadjuvant setting, resulting also in higher response rates.^{60,62-65}

Available literature shows that HT may have a beneficial effect for both treatment and palliation of relapsed GBM and AST and is a valid option for integrative cancer therapy.⁶⁸⁻⁷³ Improvements of CR, PFS, DFS, and OS are observed also for head and neck tumor treatment for HT associated with CRT and re-irradiation.⁷⁵⁻⁷⁷ In these studies, no difference in toxicity is observed and patients receiving HT reported a better quality of life, suggesting that the association of HT to CRT is a safe and effective choice of therapy for head and neck tumors.

Constant improvement of HT includes heat delivery, treatment planning, and monitoring of efficacy and toxicity. HT associated with new targeted therapies, immunotherapy, nanomedicine, or particle therapy may represent new fields of future research and clinical application.

The main limitation of this review is that the quality of the articles was not assessed as it would be in systematic review or meta-analysis.

Conclusion

There are numerous clinical studies that show good feasibility and efficacy of HT and mEHT in terms of tumor

response and survival improvements in several tumor types, such as gastrointestinal and other malignancies. HT and mEHT can be successfully applied in association with CHT, RT, and CRT for the treatment of recurrent disease.

In conclusion, HT in combination with other therapeutic modalities results in better outcomes concerning both tumor response and survival and is associated with low-grade toxicity.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Giammaria Fiorentini  <https://orcid.org/0000-0002-5615-889X>

References

1. Peeken JC, Vaupel P, Combs SE. Integrating hyperthermia into modern radiation oncology: what evidence is necessary? *Front Oncol.* 2017;7:132. doi:10.3389/fonc.2017.00132
2. Sauer R, Creeze H, Hulshof M, Issels R, Ott O; Interdisciplinary Working Group for Clinical Hyperthermia (Atzelsberg Circle) of the German Cancer Society and the German Society of Radiooncology. Concerning the final report "Hyperthermia: a systematic review" of the Ludwig

- Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. *Strahlenther Onkol.* 2012;188:209-213. doi:10.1007/s00066-012-0072-9
3. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. *Adv Exp Med Biol.* 2007;608:1-22. doi:10.1007/978-0-387-74039-3_1
 4. Hu Y, Li Z, Mi DH, et al. Chemoradiation combined with regional hyperthermia for advanced oesophageal cancer: a systematic review and meta-analysis. *J Clin Pharm Ther.* 2017;42:155-164. doi:10.1111/jcpt.12498
 5. 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. *Int J Radiat Oncol Biol Phys.* 2016;94:1073-1087. doi:10.1016/j.ijrobp.2015.12.361
 6. Szasz AM, Minnaar CA, Szentmártoni G, Szigeti GP, Dank M. Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) method: an update for the practicing oncologist. *Front Oncol.* 2019;9:1012. doi:10.3389/fonc.2019.01012
 7. Suzuki S, Masuda N, Fukuchi M, Kuwano H. Planned esophagectomy after neoadjuvant hyperthermo-chemoradiotherapy using weekly low-dose docetaxel and hyperthermia for advanced esophageal carcinomas. *Hepatogastroenterology.* 2015;62:887-891.
 8. Hulshof MCCM, Van Haaren PMA, Van Lanschoot JJB, et al. Preoperative chemoradiation combined with regional hyperthermia for patients with resectable esophageal cancer. *Int J Hyperthermia.* 2009;25:79-85. doi:10.1080/02656730802464078
 9. Sakamoto T, Katoh H, Shimizu T, et al. Clinical results of treatment of advanced esophageal carcinoma with hyperthermia in combination with chemoradiotherapy. *Chest.* 1997;112:1487-1493.
 10. Kuwano H, Sumiyoshi K, Watanabe M, et al. Preoperative hyperthermia combined with chemotherapy and irradiation for the treatment of patients with esophageal carcinoma. *Tumori.* 1995;81:18-22.
 11. Nishimura S, Saeki H, Nakanoko T, et al. Hyperthermia combined with chemotherapy for patients with residual or recurrent oesophageal cancer after definitive chemoradiotherapy. *Anticancer Res.* 2015;35:2299-2303.
 12. Sheng L, Ji Y, Wu Q, Du X. Regional hyperthermia combined with radiotherapy for esophageal squamous cell carcinoma with supraclavicular lymph node metastasis. *Oncotarget.* 2017;8:5339-5348. doi:10.18632/oncotarget.14148
 13. De Haas-Kock DFM, Buijsen J, Pijls-Johannesma M, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. *Cochrane Database Syst Rev* 2009;(3):CD006269. doi:10.1002/14651858.CD006269.pub2
 14. Gani C, Schroeder C, Heinrich V, et al. Long-term local control and survival after preoperative radiochemotherapy in combination with deep regional hyperthermia in locally advanced rectal cancer. *Int J Hyperthermia.* 2016;32:187-192. doi:10.3109/02656736.2015.1117661
 15. Zwirner K, Bonomo P, Lamprecht U, Zips D, Gani C. External validation of a rectal cancer outcome prediction model with a cohort of patients treated with preoperative radiochemotherapy and deep regional hyperthermia. *Int J Hyperthermia.* 2018;34:455-460. doi:10.1080/02656736.2017.1338364
 16. Shoji H, Motegi M, Osawa K, et al. A novel strategy of radio-frequency hyperthermia (neothermia) in combination with preoperative chemoradiotherapy for the treatment of advanced rectal cancer: a pilot study. *Cancer Med.* 2015;4:834-843. doi:10.1002/cam4.431
 17. Maluta S, Romano M, Dall'oglio S, et al. Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum. *Int J Hyperthermia.* 2010;26:108-117. doi:10.3109/02656730903333958
 18. Kato T, Fujii T, Ide M, et al. Effect of long interval between hyperthermochemoradiation therapy and surgery for rectal cancer on apoptosis, proliferation and tumor response. *Anticancer Res.* 2014;34:3141-3146.
 19. Schroeder C, Gani C, Lamprecht U, et al. Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone. *Int J Hyperthermia.* 2012;28:707-714. doi:10.3109/02656736.2012.722263
 20. Yu JI, Park HC, Choi DH, et al. Prospective phase II trial of regional hyperthermia and whole liver irradiation for numerous chemorefractory liver metastases from colorectal cancer. *Radiat Oncol J.* 2016;34:34-44. doi:10.3857/roj.2016.34.1.34
 21. Ott OJ, Schmidt M, Semrau S, et al. Chemoradiotherapy with and without deep regional hyperthermia for squamous cell carcinoma of the anus. *Strahlenther Onkol.* 2019;195:607-614. doi:10.1007/s00066-018-1396-x
 22. Liu X, Yang X, Zhou G, Chen Y, Li C, Wang X. Gemcitabine based regional intra-arterial infusion chemotherapy in patients with advanced pancreatic adenocarcinoma. *Medicine (Baltimore).* 2016;95:e3098. doi:10.1097/MD.0000000000003098
 23. Suker M, Beumer BR, Sadot E, et al. A patient-level meta analysis of FOLFIRINOX for locally advanced pancreatic cancer. *Lancet Oncol.* 2016;17:801-810. doi:10.1016/S1470-2045(16)00172-8
 24. Fiorentini G, Sarti D, Casadei V, et al. Modulated electro-hyperthermia as palliative treatment for pancreatic cancer: a retrospective observational study on 106 patients. *Integr Cancer Ther.* Published online September 27, 2019. doi:10.1177/1534735419878505
 25. Tschöep-Lechner KE, Milani V, Berger F, et al. Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer. *Int J Hyperthermia.* 2013;29:8-16. doi:10.3109/02656736.2012.740764
 26. Maluta S, Schaffer M, Pioli F, et al. Regional hyperthermia combined with chemoradiotherapy in primary or recurrent locally advanced pancreatic cancer: an open-label comparative cohort trial. *Strahlenther Onkol.* 2011;187:619-625. doi:10.1007/s00066-011-2226-6
 27. van der Horst A, Versteijne E, Besselink MGH, et al. The clinical benefit of hyperthermia in pancreatic cancer: a systematic

- review. *Int J Hyperthermia*. 2018;34:969-979. doi:10.1080/02656736.2017.1401126
28. Ohguri T, Imada H, Yahara K, Morioka T, Nakano K, Korogi Y. Concurrent chemoradiotherapy with gemcitabine plus regional hyperthermia for locally advanced pancreatic carcinoma: initial experience. *Radiat Med*. 2008;26:587-596. doi:10.1007/s11604-008-0279-y
 29. Datta NP, Pestalozzi B, Clavien PA, et al; Members of the HEATPAC Trial Group. "HEATPAC"—a phase II randomized study of concurrent thermochemoradiotherapy versus chemoradiotherapy alone in locally advanced pancreatic cancer. *Radiat Oncol*. 2017;12:183. doi:10.1186/s13014-017-0923-8
 30. Volovat C, Volovat SR, Scripcaru V, Miron L. Second-line chemotherapy with gemcitabine and oxaliplatin in combination with loco-regional hyperthermia (EHY-2000) in patients with refractory metastatic pancreatic cancer—preliminary results of a prospective trial. *Rom Rep Phys*. 2014;66:166-174. http://rrp.infm.ro/2014_66_1/A18.pdf
 31. NCCN Guidelines. www.nccn.org/professionals/physician_gls/pdf/breast.pdf
 32. Kouloulis V, Triantopoulou S, Uzunoglou N, et al; Greek Society of Hyperthermic Oncology. Hyperthermia is now included in the NCCN clinical practice guidelines for breast cancer recurrences: an analysis of existing data. *Breast Care (Basel)*. 2015;10:109-116. doi:10.1159/000376594
 33. Lee SY, Lee NR, Cho DH, Kim JS. Treatment outcome analysis of chemotherapy combined with modulated modulated electrohyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. *Oncol Lett*. 2017;14:73-78. doi:10.3892/ol.2017.6117
 34. Brüningk SC, Ijaz J, Rivens I, Nill S, Ter Haar G, Oelfke U. A comprehensive model for heat-induced radio-sensitisation. *Int J Hyperthermia*. 2018;34:392-402. doi:10.1080/02656736.2017.1341059
 35. Baronzio G, Gramaglia A, Fiorentini G. Hyperthermia and immunity. A brief overview. In *Vivo*. 2006;20(6A):689-695.
 36. Takeda T, Takeda T, Etani M, Kobayashi S, Takeda H. The effect of immunotherapy and hyperthermia on patients with advanced or recurrent breast cancer [in Japanese]. *Gan To Kagaku Ryoho*. 2013;40:1596-1599.
 37. Klimanov MY, Syvak LA, Orel VE, et al. Efficacy of combined regional inductive moderate hyperthermia and chemotherapy in patients with multiple liver metastases from breast cancer. *Technol Cancer Res Treat*. Published online October 18, 2018. doi:10.1177/1533033818806003
 38. Oldenborg S, Van Os RM, Van rij CM, et al. Elective re-irradiation and hyperthermia following resection of persistent locoregional recurrent breast cancer: a retrospective study. *Int J Hyperthermia*. 2010;26:136-144. doi:10.3109/02656730903341340
 39. Linthorst M, Baaijens M, Wiggenraad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: results in 248 patients. *Radiother Oncol*. 2015;117:217-222. doi:10.1016/j.radonc.2013.05.010
 40. Oldenborg S, Griesdoorn V, Os R, et al. Re-irradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: size matters. *Radiother Oncol*. 2015;117:223-228. doi:10.1016/j.radonc.2015.10.017
 41. Linthorst M, van Geel AN, Baaijens M, et al. Re-irradiation and hyperthermia after surgery for recurrent breast cancer. *Radiother Oncol*. 2013;109:188-193. doi:10.1016/j.radonc.2013.05.010
 42. De-Colle C, Weidner N, Heinrich V, et al. Hyperthermic chest wall re-irradiation in recurrent breast cancer: a prospective observational study. *Strahlenther Onkol*. 2019;195:318-326. doi:10.1007/s00066-018-1414-z
 43. Refaat T, Sachdey S, Sathiascelan V, et al. Hyperthermia and radiation therapy for locally advanced or recurrent breast cancer. *Breast*. 2015;24:418-425. doi:10.1016/j.breast.2015.03.008
 44. Varma S, Myerson R, Moros E, Taylor M, Straube W, Zoberi I. Simultaneous radiotherapy and superficial hyperthermia for high-risk breast carcinoma: a randomised comparison of treatment sequelae in heated versus non-heated sectors of the chest wall hyperthermia. *Int J Hyperthermia*. 2012;28:583-590. doi:10.3109/02656736.2012.705216
 45. Burchardt E, Roszak A. Hyperthermia in cervical cancer—current status. *Rep Pract Oncol Radiother*. 2018;23:595-603. doi:10.1016/j.rpor.2018.05.006
 46. Lutgens LC, Koper PC, Jobsen JJ, et al. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: results of the randomized RADCHOC trial. *Radiother Oncol*. 2016;120:378-382. doi:10.1016/j.radonc.2016.02.010
 47. Ohguri T, Harima Y, Imada H, et al. Relationships between thermal dose parameters and the efficacy of definitive chemoradiotherapy plus regional hyperthermia in the treatment of locally advanced cervical cancer: data from a multicentre randomised clinical trial. *Int J Hyperthermia*. 2018;34:461-468. doi:10.1080/02656736.2017.1352105
 48. Datta NR, Rogers S, Klingbiel D, Gómez 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;32:809-821. doi:10.1080/02656736.2016.1195924
 49. Harima Y, Ohguri T, Imada H, et al. A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer. *Int J Hyperthermia*. 2016;32:801-808. doi:10.1080/02656736.2016.1213430
 50. Heijkoop ST, van Doorn HC, Stalpers LJ, et al. Results of concurrent chemotherapy and hyperthermia in patients with recurrent cervical cancer after previous chemoradiation. *Int J Hyperthermia*. 2014;30:6-10. doi:10.3109/02656736.2013.844366
 51. Westermann A, Mella O, Van Der Zee J, et al. Long-term survival data of triple modality treatment of stage IIB-III-IVA cervical cancer with the combination of radiotherapy, chemotherapy and hyperthermia—an update. *Int J Hyperthermia*. 2012;28:549-553. doi:10.3109/02656736.2012.673047
 52. Minnaar CA, Kotzen JA, Ayeni OA, et al. The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: early results from a phase III randomised controlled trial. *PLoS One*. 2019;14:e0217894. doi:10.1371/journal.pone.0217894
 53. Heijkoop ST, Franckena M, Thomeer MG, Boere IA, Van Montfort C, Van Doorn HC. Neoadjuvant chemotherapy

- followed by radiotherapy and concurrent hyperthermia in patients with advanced-stage cervical cancer: a retrospective study. *Int J Hyperthermia*. 2012;28:554-561. doi:10.3109/02656736.2012.674622
54. Franckena M, Fatehi D, de Bruijne M, et al. Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. *Eur J Cancer*. 2009;45:1969-1978. doi:10.1016/j.ejca.2009.03.009
55. Lassche G, Crezee J, Van Herpen CML. Whole-body hyperthermia in combination with systemic therapy in advanced solid malignancies. *Crit Rev Oncol Hematol*. 2019;139:67-74. doi:10.1016/j.critrevonc.2019.04.023
56. Longo TA, Gopalakrishna A, Tsvian M, et al. A systematic review of regional hyperthermia therapy in bladder cancer. *Int J Hyperthermia*. 2016;32:381-389. doi:10.3109/02656736.2016.1157903
57. Datta NR, Stutz E, Puric E, et al. A pilot study of radiotherapy and local hyperthermia in elderly patients with muscle-invasive bladder cancers unfit for definitive surgery or chemoradiotherapy. *Front Oncol*. 2019;9:889. doi:10.3389/fonc.2019.00889
58. Inman BA, Stauffer PR, Craciunescu OA, Maccarini PF, Dewhirst MW, Vujaskovic Z. A pilot clinical trial of intravesical mitomycin-C and external deep pelvic hyperthermia for non-muscle-invasive bladder cancer. *Int J Hyperthermia*. 2014;30:171-175. doi:10.3109/02656736.2014.882021
59. Geijsen ED, de Reijke TM, Koning CC, et al. Combining mitomycin C and regional 70 MHz hyperthermia in patients with non muscle invasive bladder cancer: a pilot study. *J Urol*. 2015;194:1202-1208. doi:10.1016/j.juro.2015.05.102
60. Fendler WP, Lehmann M, Todica A, et al. PET response criteria in solid tumors predicts progression-free survival and time to local or distant progression after chemotherapy with regional hyperthermia for soft-tissue sarcoma. *J Nucl Med*. 2015;56:530-537. doi:10.2967/jnumed.114.152462
61. Angele MK, Albertsmeier M, Prix NJ, et al. Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection: a subgroup analysis of a randomized phase-III multicenter study. *Ann Surg*. 2014;260:749-756. doi:10.1097/SLA.0000000000000978
62. Issels RD, Lindner LH, Verweij J, et al; European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology. 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;4:483-492. doi:10.1001/jamaoncol.2017.4996
63. Schlemmer M, Wendtner CM, Lindner L, Abdel-Rahman S, Hiddemann W, Issels RD. Thermochemotherapy in patients with extremity high-risk soft tissue sarcomas (HR-STs). *Int J Hyperthermia*. 2010;26:127-135. doi:10.3109/02656730903335995
64. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol*. 2010;11:561-570.
65. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a "state of the science" review. *Neuro Oncol*. 2014;16:896-913. doi:10.1093/neuonc/nou087
66. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol*. 2012;14(suppl 5):v1-v49. doi:10.1093/neuonc/nos218
67. Venur VA, Peereboom DM, Ahluwalia MS. Current medical treatment of glioblastoma. *Cancer Treat Res*. 2015;163:103-115. doi:10.1007/978-3-319-12048-5_7
68. 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. doi:10.1136/bmjopen-2017-017387
69. Fiorentini G, Sarti D, Milandri C, et al. Modulated electrohyperthermia in integrative cancer treatment for relapsed malignant glioblastoma and astrocytoma: retrospective multicenter controlled study. *Integr Cancer Ther*. Published online December 22, 2018. doi:10.1177/1534735418812691
70. Fiorentini G, Sarti D, Milandri C, et al. *Modulated Electrohyperthermia for the Treatment of Relapsed Brain Gliomas*. In: Andras S, ed. *Challenges and Solutions of Oncological Hyperthermia*. Cambridge Scholars Publishing, 2020.
71. Heo J, Kim SH, Oh YT, Chun M, Noh OK. Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas. *Neoplasma*. 2017;64:803-808. doi:10.4149/neo_2017_520
72. Fiorentini G, Sarti D, Milandri C, Dentico P, Mambrini A, Guadagni S. Retrospective observational clinical study on relapsed malignant gliomas treated with electro-hyperthermia. *Int J Neurooncol Brain Tumor*. 2017;1:9-13. <https://www.scireslit.com/Neurooncology/IJNBT-ID12.pdf>
73. Wismeth C, Dudel C, Pascher C, et al. Transcranial electrohyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas: phase I clinical results. *J Neurooncol*. 2010;98:395-405. doi:10.1007/s11060-009-0093-0
74. Datta NR, Rogers S, Ordonez SG, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: a systematic review and meta-analysis. *Int J Hyperthermia*. 2016;32:31-40. doi:10.3109/02656736.2015.1099746
75. 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;14:7395-7400. doi:10.7314/APJCP.2013.14.12.7395
76. Hua Y, Ma S, Fu Z, Hu Q, Wang L, Piao Y. Intracavity hyperthermia in nasopharyngeal cancer: a phase III clinical study. *Int J Hyperthermia*. 2011;27:180-186. doi:10.3109/02656736.2010.503982
77. 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;90:853-858. doi:10.3109/09553002.2014.916579
78. De Wee E, Verduijn GM, Rijnen Z, et al. OC-0335: feasibility of deep head and neck hyperthermia. *Radiother Oncol*. 2015;115(suppl 1):S165-S166. doi:10.1016/S0167-8140(15)40333-0