Locoregional Hyperthermia in Cancer Care

Healthcare Provider Resource

Developed by:
The Patterson Institute for Integrative Oncology Research of the Canadian College of Naturopathic Medicine

Last updated: December 2023

CCNM | Patterson Institute for Integrative Oncology Research

THE CENTRE FOR HEALTH INNOVATION

Table of Contents

General Information 4
Summary 4
Background 4
Types of hyperthermia 5
Heating Systems 5
Methods 5
Mechanism of Action 6
Clinical Evidence for Effectiveness 7
Bladder Cancer 8
Brain Cancer 9
Breast Cancer 9
Cervical Cancer 10
Colorectal & Anal Cancer 14
Rectal cancer: 14
Colorectal Cancer (Mixed) 15
Anal Cancer 16
Esophageal Cancer 16
Gastric Cancer 17
Head and Neck Cancer 19
Hepatobiliary Cancer 21
Hodgkin's Lymphoma/Disease 21
Lung Cancer 22
Melanoma 25
Ovarian Cancer 26
Pancreatic Cancer 27
Prostate Cancer 30
Sarcomas and Soft-Tissue Tumors 31
Vulvar & Vaginal 34
Studies Including Mixed Cancer Types 34
Abdominal and Pelvic Tumors 34
Genitourinary Cancers 35
Peritoneal Carcinomatosis 36
Liver Metastases 36
Cervical Lymph Node Metastases 36
Brain Metastases 37

Superficial Tumors 37
Mixed Advanced Cancers 38
Miscellaneous Mixed Cancers 39
Other Studies Not Described in Detail 39
Quality of Life Support & Symptom Management 39
Hyperthermia as Monotherapy 40
Table 1: Systematic Reviews and Meta-Analyses of LRHT for Cancer 41
Table 2: Randomized Controlled Trials of LRHT For Cancer 43
Safety 52
Adverse Effects: 52
Physiological Effects During and After Regional Hyperthermia: 52
Interactions: 53
Chemotherapy: 53
Radiotherapy: 53
Targeted Therapies and Endocrine Therapies: 53
Other Medications: 54
Other CAM Therapies: 54
Cautions and Contraindications: 54
Practical Aspects of Hyperthermia Treatment 55
Treatment Planning and Monitoring: 55
Treatment Team: 55
Timing with Other Cancer Therapies: 55
Treatment Temperature: 56
Treatment Time: 56
Treatment Frequency and Duration of Use: 56
Power: 56
Devices and Technology: 56
Availability and Cost of Treatment in Canada: 57
Disclaimer 57
References 58

General Information

Name of therapy: Locoregional hyperthermia (LRHT)

Alternate names: Local regional hyperthermia, local hyperthermia (LHT), regional hyperthermia (RHT), modulated electro-hyperthermia (mEHT), locoregional oncothermia, oncothermia

Not synonymous with: Whole body hyperthermia, isolated limb perfusion, hyperthermic intraperitoneal chemotherapy (HIPEC), intraoperative hyperthermia, thermal ablation, sauna

Common uses in cancer care: As a chemosensitizer and radiosensitizer to improve cancer outcomes including objective response, disease-free survival, and overall survival.

Summary

Hyperthermia (HT) in cancer management refers to the external application of heat to raise intratumoral temperature to 39-44°C. Various types of hyperthermia exist including local hyperthermia, regional hyperthermia, whole-body hyperthermia, interstitial and endocavitary hyperthermia, hyperthermic isolated limb perfusion, hyperthermic intraperitoneal chemotherapy (HIPEC) and hyperthermic intravesical chemotherapy (HIVEC). The most used technologies to induce hyperthermia include radiofrequency, microwave, or ultrasound. Local and regional hyperthermia (locoregional; LRHT) are among the most used and studied and are the focus of this monograph. HT is purported to have several mechanisms of action through which it may act against cancer including physiological changes such as vasodilation, direct cytotoxic effects, chemosensitizing and radiosensitizing actions, and immune modulation. LRHT is used primarily as an adjunct to chemotherapy and radiotherapy due to its ability to sensitize malignant tissues to these treatments. Various studies have demonstrated improved outcomes for patients treated with HT alongside chemo-and/or-radiotherapy. The best evidence for improved disease control and survival are for breast cancer (locally recurrent), cervical cancer, esophageal and gastric cancers, head and neck squamous cell carcinoma, and high-risk soft tissue sarcoma. Research related to quality of life (QOL) is limited, and thus not a primary indication. Hyperthermia with modern technology and treatment planning is generally well tolerated; the most common side effects are discomfort, mild pain, local erythema, and thermal skin burns. Less commonly, subcutaneous burns are a possible adverse effect. Despite promising research, trial heterogeneity and methodological concerns limit the strength of the conclusions that can be drawn. In the future, more high-quality studies with proper quality assurance and treatment planning are needed to ensure consistency and reproducibility.

Background

Hyperthermia (HT) for cancer involves increasing cell and tissue temperatures to levels that are higher than usually maintained, via exogenously generated means, to selectively affect tumors. It is usually applied in conjunction with conventional care (e.g. chemotherapy and/or radiation).[1] Documented HT use dates back to the 1700s when remissions of certain cancers were noted in patients with fever-inducing bacterial infections. This led to experimentation with vaccines to induce fever, leading to a 20% cure rate in

patients with unresectable sarcoma.[2] In the latter half of the 20th century, preclinical studies and preliminary clinical trials of LRHT applied to patients with cancer demonstrated synergistic effects with radiation and chemotherapy.[3,4] Technological challenges to producing safe and consistent tissue heating were limitations of early trials and clinical application. Since then, however, newer equipment and monitoring devices have been developed in the 21st century.[4]

Types of hyperthermia

Several types of HT have been used in oncology: local hyperthermia (LHT), regional hyperthermia (RHT), interstitial and endocavitary hyperthermia, whole-body hyperthermia, hyperthermic isolated limb perfusion,[5] hyperthermic intraperitoneal chemotherapy (HIPEC), and hyperthermic intravesical chemotherapy (HIVEC).[6]

LHT increases the temperature of superficial tumors by applying applicators or antennae on the skin surface with a contact medium.[6] The applicators most often emit microwaves or radiowaves to heat the tumor.[5] Interstitial and endocavitary hyperthermia utilize antennas or applicators implanted within the tumor or inserted in anatomical openings of hollow organs such as the rectum or vagina,[5] and thus heat is applied internally. In RHT, deep tumors can be heated by arrays of antennas; antenna pairs may be arranged in a ring around the patient.[5] Whole-body hyperthermia strives to raise the core body temperature to 42°C for 1-hour. This type of treatment requires close medical supervision, and often requires analgesia or sedation.[5] Hyperthermic isolated limb perfusion is a surgical procedure providing heated chemotherapy to tumors without reaching systemic circulation.[5,7] HIPEC and HIVEC treatments involve infusing heated chemotherapy agents into the abdominal cavity or bladder.[6]

This monograph focuses exclusively on externally applied local and regional hyperthermia (also known as locoregional hyperthermia; LRHT). For ease of reading, LRHT will also be referred to as “hyperthermia” (HT) throughout this monograph.

Heating Systems

Multiple heating systems exist which manipulate different forms of physical energy to induce tissue temperature changes. The four most commonly utilized physical means to induce hyperthermia include capacitive heating, radiative heating, ultrasound, and infrared-A.[2,8] Capacitive heating systems work by directing an electrical current between two electrodes placed on opposite parts of a body region, utilizing direct body contact using a water bolus medium.[2] This system tends to create high power heating densities around the bolus’ edges and wide coverage of adipose layers.[2] Radiative heating systems utilize radiowaves and microwaves, with frequencies ranging from 75-915MHz, yielding a better temperature distribution.[2] Water filtered infrared-A HT uses a halogen lamp passing through a water filter for superficial tumors.[8] Ultrasound creates a mechanical wave that generates heat through mechanical friction.[9] HT in clinical use and research is most commonly induced by microwave, radiofrequency, or ultrasound and uses capacitive or radiative systems.[9]

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research and are updated approximately every two years. Comprehensive and structured literature searches are performed in Medline

and Cochrane library from inception to August 16, 2022, for English-language studies in people with cancer. Additional scoping reviews are performed by research staff to obtain supporting information such as background, mechanism of action, and safety data. Articles are duplicate-screened, data is extracted into standardized spreadsheets, and studies are summarized using descriptive statistics. Studies that are reviewed in a systematic review are not-reviewed again in this monograph.

Mechanism of Action

Multiple mechanisms of action are proposed in the literature to explain the observed effects of HT for patients with cancer. Broadly, mechanisms include direct effects of heat including vascular vasodilation and direct thermal toxicity, radiosensitization, chemosensitization, and immune-mediated effects.

HT invokes direct effects on atypical tumor vasculature and hemodynamics.[2,6] Temperatures between 37°C to 42°C result in local vascular dilation, resulting in increased vascular perfusion and oxygenation which can mitigate inflammation and deep tissue hyperemia in hypoxic tumor tissue.[6] Temperatures > 42°C cause damage to tumor vasculature via fluid and protein accumulation within the microenvironment which lead to compression and vascular perfusion reduction, while also dampening tumor growth and proliferation capabilities.[6] At temperatures > 42.5°C, direct thermal toxicity can kill cells due to denaturation of structural proteins.[10] Alterations in tissue perfusion, and consequently oxygenation, have been proposed as one of the principal therapeutic effects of HT in the context of cancer. Hypoxia within tumors is associated with poor prognosis and resistance to both radiotherapy and chemotherapy. Furthermore, hypoxia is associated with malignant progression, further local invasion, and may facilitate metastasis.[11] As hypoxia is implicated in cancer progression, tumor oxygenation has been a focus for HT targeting. There is uncertainty regarding the duration of increased tumour oxygenation from HT, with many studies showing cessation of oxygenation shortly after cessation of treatment, while some have shown improved oxygenation lasting 24-48h after low-dose heating.[11] Firm conclusions regarding degree and duration of oxygenation changes within tumor architecture are difficult to describe as inconsistent findings are common between similar studies. Future, well-designed studies, using improved models, will allow for a clearer understanding of this observed effect to be described.

The potential for HT to augment the effects of chemotherapy and radiation therapy has led to the development of combination treatment interventions in experimental design studies.[2,6,10,11] Several additive and synergistic effects have been proposed for concurrent application of chemotherapy with HT. For one, the increase in tissue temperature leads to vasodilation which can enhance drug delivery to the tumour.[10] The increased temperature can also lead to higher cell permeability, which may in turn facilitate better drug delivery coupled with cell membrane changes which may increase drug uptake in cancer cells.[6] Certain chemotherapy drugs appear to have enhanced cytotoxicity in the presence of heat (e.g. cyclophosphamide, ifosfamide). Mechanisms whereby this may occur is via increased alkylation, increased cell drug uptake and augmentation of chemotherapy induced cell damage.[12]

HT has been proposed to improve response to radiation therapy through several pathways. Hypoxic

tumor environments are associated with radioresistance,[2] therefore, the capacity for HT to offset hypoxia, and improve perfusion/oxygenation, may circumvent this cancer related protective factor.[2,6,10] It is important to note, however, that the therapeutic window of HT in this context may be narrow. Excessively high temperatures (>43^0C) may damage blood vessels, thereby reducing perfusion and intensifying hypoxia.[6] Elevated cell temperatures may suppress DNA damage repair[2] and interfere with telomere prolongation (via heat induced shock protein 70 production), thus possibly enhancing the proapoptotic effects of radiation.[6] Additionally, elevated tissue temperature may increase cellular and mitochondrial membrane permeability, leading to altered Ca^{2+} spikes resulting in rapid accumulation of reactive oxygen species, further supporting the direct cellular damaging effects of radiation.[2] The greatest radiosensitization effect occurs when RT and HT are given simultaneously, with effectiveness declining the further apart these treatments are administered.[10]

An emerging area of research regarding the mechanism of action of HT involves immune mediated responses to tissue temperature changes.[2,6,13] HT appears to trigger both innate and adaptive immune system activity[10], including increased expression of immunogenic surface receptors, enhanced NK and CD8+ cells, activation of macrophages, and increased immune cell migration via augmented perfusion and permeability.[2,6] Additionally, in response to induced HT, heat shock proteins (HSPs) are released, which along with tumor antigens act as danger signals outside the cell and activate and attract dendritic cells. Dendritic cells take up tumor antigen to present and prime cytotoxic T lymphocytes, thus facilitating antitumor immunity.[10] The latter may be important with an augmentation to the abscopal effect that has been proposed with radiotherapy[10] and recently reported to be enhanced in cervical cancer treated with HT and RT.[14]

Issels et al (2016)[15] proposed six hallmarks of HT as a treatment approach to describe its pleiotropic effects. These hallmarks have all been described above but are organized differently here. The six proposed hallmarks are: (1) blocking cell survival (cytotoxic effects), (2) inducing cellular stress response (intracellular expression of heat shock proteins), (3) modulating immune response (enhancing cancer antigen recognition), (4) evading DNA repair (suppressing action of DNA repair mechanisms), (5) changing the tumor microenvironment (effects on tumor vasculature, reactive oxygen species, metabolic alterations), and (6) sensitization to chemotherapy and radiotherapy.

Clinical Evidence for Effectiveness

Human studies in cancer-populations evaluating HT, including systematic reviews and meta-analyses, randomized controlled trials (RCTs), observational studies, and single-arm trials, are reviewed below. The evidence is organized alphabetically by cancer type, with studies including mixed cancers at the end. For each cancer type, a brief summary of the evidence is provided first, labelled '*Evidence at A Glance*', followed by a more detailed description of the included studies. The details for all systematic reviews and meta-analyses are further described in Table 1, and RCTs in Table 2. There were 182 studies eligible for inclusion. Of the 182 studies, the majority were single-arm or observational trials. However, 7 systematic reviews (including 37 RCTs) and 20 additional RCTs (not included in a systematic review) were identified.

In summary, there is reasonable or strong evidence of improved disease outcomes (response rates, disease free survival, or overall survival) for patients with the following cancer types treated with HT combined with chemo-and/or-radiotherapy: locally recurrent breast cancer, cervical cancer, esophageal cancer, gastric cancer, head and neck squamous cell carcinoma, and high-risk soft tissue sarcoma. Evidence is more variable and/or limited for other cancer types. Clinical effectiveness has only been demonstrated for the application of hyperthermia with chemotherapy and/or radiotherapy.[16,17] Research related to QOL is limited and of generally poor quality, and thus not the primary indication for clinical use. Although there have been some good quality studies, overall methodological quality is a concern, and additional large, randomized controlled trials are needed to confirm or prove efficacy.

Bladder Cancer

Evidence at a glance:

One systematic review[18] of 15 studies (1 RCT, 1 non-randomized trial, 7 single-arm trials, 6 observational studies), two single-arm trials[19,20], and one retrospective study[21] were identified. Owing to research limitations, heterogenous design, and methodological deficits, no clear conclusions can be drawn for predicting the effects of HT for bladder cancer. However, the totality of evidence indicates a trend for beneficial effects of HT in patients with bladder cancer, especially when combined with conventional care. Application of HT in bladder cancer deserves further rigorous investigation.

The systematic review included 15 studies (n = 346) that investigated the application of HT for both non-muscle invasive (NMIBC) and muscle invasive bladder cancer (MIBC).[18] One RCT (n = 101) which applied RHT and radiation for MIBC reported that the combination did not significantly improve overall survival compared to monotherapy (28% vs 22%, respectively, $p > 0.05$). One non-randomized clinical trial reported a complete response rate of 54.5% for patients with NMIBC receiving RHT and doxorubicin compared to 35% in those only receiving chemotherapy (statistical analysis for significance was not performed). Two pilot studies reported on recurrence free survival at 24 months in patients with NMIBC receiving HT and intravesical mitomycin, with one reporting a rate of 78% and the other 33%. Multiple less rigorous clinical trials and pilot studies examined similar patient groups, with mixed results and often non-significant findings. Two studies looked specifically at RHT in combination with intravenous chemotherapy, with one reporting 2/4 participants experiencing partial response lasting 5 and 7 months, and the other reporting that 2/27 experienced complete response and 7/27 partial response. One well described study involving 19 patients with MIBC and NMIBC receiving trans-urethral resection with RHT reported a complete response rate of 96% and recurrence free survival of 81% at three years.[18]

Two single arm[19,20] studies and one retrospective observational[21] study were also identified which were not included in the systematic review.[18] The observational study (n=369) reported that in patients with bladder cancer undergoing post-transurethral resection, the addition of HT to radiotherapy and chemotherapy did not significantly improve complete response ($p=0.092$), but did improve overall survival ($p=0.0001$) and 5 & 10 year disease free survival ($p=0.0001$).[21] One of the single arm trials (n=20)[20] which applied HT and radiation, post-transurethral resection, reported a 3-year bladder

preservation rate of 86.6% and that 11/20 were still alive at time of publication. The second single arm trial (n=16) in patients with MIBC, not eligible for surgery and/or chemoradiotherapy, reported that all participants had an initial response to HT combined with radiation, and a cause-specific local disease free survival rate of 64.3%, with 6/16 experiencing recurrence by 19 months follow-up.[19]

Brain Cancer

Evidence at A Glance:

Two controlled, retrospective observational studies (one in recurrent glioblastoma[22] and one in relapsed glioma or astrocytoma[23]), and one small single-arm trial of high-grade glioma[24] were identified. Research for the use of HT for patients with brain cancer is limited. Based on a few studies of varying methodological strength, HT may complement standard treatment of glioblastoma and astrocytoma, but results should be interpreted with caution.

An observational study (n=168) retrospectively included participants with recurrent glioblastoma, either receiving dose dense temozolomide alone or in combination with HT, Boswellia caterii, mistletoe and selenium.[22] Mean survival (7.16 months) in the HT arm was not significantly different than control (95% CI 6.25-8.08, p = 0.531). It was reported that the hyperthermia group experienced significantly fewer instances of grade III-IV toxicity than control subjects.

The second observational study included 149 patients with relapsed glioma (n = 111) or astrocytoma (n=38), comparing best supportive care with and without HT.[23] The authors reported that the overall response rate was significantly better in the HT group compared to the supportive care group for patients with astrocytoma (72% vs 37%, $p < 0.05$), there was also a statistically significant increase in median overall survival for the HT group (16.5 months, range 3-156 months) compared to control (16 months, range: 3-120 months) ($p = 0.0065$) , although the absolute difference was small. The response rate for the GBM group was significantly higher in the HT group (19% difference), with the median overall survival significantly better for the GBM group (14 months) compared to control (9 months) ($p = 0.047$).

A small single-arm trial investigated the use of a non-invasive electro hyperthermia device for patients with either high-grade glioma or glioblastoma receiving alkylating chemotherapy.[24] Median time to progression was 14 weeks, with a median overall survival of 81 weeks from diagnosis.

Breast Cancer

Evidence at A Glance:

One meta-analysis of 34 studies[25] , two single-arm trials[26,27] and two case series [28,29] were identified for breast cancer and HT. For patients with locally recurrent breast cancer receiving radiation therapy, the addition of hyperthermia likely confers benefit for complete response and disease control based on results of a meta-analysis.[25] Less is known about the use and effects of HT for patients with different breast cancer presentations (e.g., metastatic disease, and first line treatment).

The meta-analysis included 31 articles (reporting on 34 studies), including 5 RCTs, 3 non-randomized controlled trials, and 26 single-arm trials, all of which investigated the addition of HT to radiation for locally

recurrent breast cancer.[25] The median number of HT treatments was 7 with a mean planned target tissue temperature of 42.5 °C . Most studies applied HT twice per week immediately after radiation therapy. Based on the controlled clinical trials, the complete response rate was 60.2% in the combination group compared to 38.1% in the control group (OR 2.64; 95% CI 1.66-4.18, p < 0.0001). Based on single-arm trials, the complete response rate was reported to be 63.4% (event rate 0.64; 95% CI 0.57-0.66). Mean acute, and late grade III/IV toxicities were higher in the hyperthermia group compared to control (14.4% vs 5.2%). Authors note that due to heterogeneity of studies, and that publication dates spanned 34 years, no uniform toxicity scoring criteria could be presented.

Two single arm studies not included in the meta-analysis were identified.[26,27] The first combined and reported on two phase I single-arm studies including 29 patients with chest-wall recurrences from breast cancer, all of which had received prior treatment (hormone therapy, radiation and/or chemotherapy).[26] In both applications, HT was delivered within 30-60 minutes of low-temperature liposomal doxorubicin, resulting in an observed grouped local response rate of 48.3%, with 17.2% having complete response. All adverse events were reported to be chemotherapy related. The second small (n=7) single arm trial applied a combination of chemotherapy (paclitaxel) and HT simultaneously for patients with recurrent, inoperable, breast cancer who had already received prior conventional care.[27]All participants experienced an objective response, with 4 complete local responses and 3 partial local responses. Median time to recurrence for those who relapsed was 6 months.

Two case series were identified. In the first one, 53 patients with triple negative breast cancer (TNBC) stage I-IIIB with residual disease after neoadjuvant chemotherapy were treated with adjuvant chemotherapy (gemcitabine + cisplatin) and twice weekly regional hyperthermia.[28] Overall survival (OS) and disease-free-survival (DFS) at 3 years were 81.6% and 57.5%, respectively. The treatment was well tolerated; reported grade 3/4 toxicities were leukopenia (38%), grade 3 elevation of transaminases (ALT/AST) (6%), thrombocytopenia (4%), and anemia (4%). Another case series of ten patients with advanced metastatic or recurrent breast cancer who were considered incurable by the use of conventional treatment received mEHT either alone (4 patients) or with additional adjuvant therapies (6 patients) for a duration ranging between 4-30 weeks.[29] Partial response was achieved in 30%, stable disease in 30%, and progressive disease in 40% of patients, with no adverse effects identified. These results support the feasibility of using mEHT in this population for a relatively long duration without side effects.

Cervical Cancer

Evidence at A Glance:

Two systematic reviews with meta-analysis[30,31] (reporting on 7 RCTs), 7 publications on 4 RCTs ,[14,32-37] and 6 single-arm trials were included.[38-43] Overall, there is consistent and strong evidence that the addition of LRHT to radiation therapy and chemoradiation for patients with stage II-IVa cervical cancer is beneficial. Further studies are warranted to determine the magnitude of effect and unique subgroups of patients that may benefit the most from the addition of HT. No differences

in toxicity were noted between control and HT groups across most studies.

A systematic review and meta-analysis of LRHT by the Cochrane group for patients with locally advanced (stage IIb-IVa) cervical cancer was published in 2016.[30] A conventional meta-analysis included 6 RCTs (n = 427) comparing hyperthermia-radiotherapy (HTRT) to radiotherapy (RT), and a network meta-analysis (7 RCTs, n = 1160) compared four treatment options: hyperthermia-chemotherapy-radiotherapy (HTCRT), HTRT, chemotherapy-radiotherapy (CRT) and RT. The conventional meta-analysis found that HTRT outperformed RT for complete response (CR) and long-term locoregional control (OR 2.67, 95% CI 1.57-4.54, p < 0.001, and OR 2.61, 95% CI 1.55–4.39, p < 0.001 respectively). Overall survival was also superior in the HTRT group compared to RT (OR 1.94, 95% CI 1.10-3.40, p = 0.021), however when analyzed as a risk difference the result was no longer significant (8.4% advantage, p = 0.299). There was no significant difference in toxicities between groups. The network meta-analysis looked only at two outcomes: CR and survival at end of study. HTCRT was superior to CRT (OR 2.91, 95% CI 1.97-4.31), and RT (OR 4.52, 95% CI 1.93-11.78) for CR rates. For overall survival at end of study, HTCRT was superior to CRT (OR 2.65, 95% CI 1.51-4.87) and RT (OR 5.57, 95% CI 1.22-23.42). Relative rankings based on rankogram and surface under cumulative ranking curve indicated the best option for treatment was HTCRT, followed by HTRT and CRT which were nearly identical, and finally RT. Hyperthermia was usually administered immediately after RT for approximately 1 hour, to achieve tissue temperature of 40-43°C. In summary, this meta-analysis indicates that HTRT is superior to RT alone for locally advanced cervical cancer, and some evidence from the network meta-analysis indicates that HTCRT may be the most efficacious approach for these patients, but more research is needed. The Cochrane group had previously published a systematic review and meta-analysis of HT for cervical cancer in 2010.[31] This review included the same six RCTs for HTRT vs RT for FIGO stage IIb-IVa cervical cancer as the 2016 meta-analysis, and thus results will not be summarized again. In summary, the findings were consistent with the more recent systematic review and meta-analysis.[30] The authors noted that there were methodological flaws in the studies included and there was over-representation of stage IIIb which may impact the generalizability to other stages considered locally advanced. Thus, the authors recommend further studies to provide a definitive conclusion.

Seven publications on four controlled trials have been published since the last systematic review.[14,32-35],[36,37]All but one studied the effect of HT with chemoradiotherapy (CRT) in patients with stage IB-IV cervical cancer. The first was a multicentre RCT which included 101 treatment naive patients, and reported that the addition of once weekly HT to CRT (cisplatin) did not improve overall 5-year-survival (adjusted HR 0.485, 95% CI 0.217-1.082, p = 0.077), disease free survival (adjusted HR 0.517, 95% CI 0.251-1.065, p = 0.073), local relapse-free survival (p > 0.05) or complete response (p > 0.05) compared to CRT alone.[32] Multivariate adjusted analysis (adjusted for age, FIGO stage, histology) showed a trend towards improved response rate in patients with locally advanced disease (OR 3.993; 95% CI 1.018-15.670, p = 0.047). Adverse events were similar between groups. A second similar RCT (n = 435) analyze results per-protocol and as intention to treat (ITT).[36] In the PP analysis, the HT+CRT

group demonstrated significantly better 5-year OS (81.9% vs. 72.3%, P = 0.040) compared to the CRT group; however, the 5-year local relapse-free survival was not significantly different (86.8% vs 82.7%, P = 0.27). There was no significant difference between groups regarding acute and late toxicity. Similar, but not statistically significant, results were reported with the ITT analysis. Further analysis revealed that CRT alone, compared to HT+CRT, was associated with a significantly higher risk of death in the PP group for both the univariate (P = 0.043) and multivariate (P = 0.045) analyses and in the multivariate analysis for ITT (P = 0.043).

Four papers were published with data from the same phase III RCT looking at the effect of mEHT with CRT, compared to CRT alone for patients with stage IIB-IIIB cervical cancer.[14,33,35,37] Patients (n = 210) who were recruited from a low-resource population in Africa, were treated with mEHT twice weekly immediately before radiation treatment, and also received cisplatin-chemotherapy. The primary outcome was local disease control (LDC), and secondary outcomes included toxicity, QOL, 2-year survival, and cost effectiveness. The first publication reported results from an early analysis of 6-month LDC and survival.[33] At 6 months, the LDC and local DFS were superior in the mEHT group compared to the control group (45.5% vs 24.1%, p = 0.003; 38.6% vs 19.8%, p = 0.003 respectively). The second publication reported on toxicity and quality of life.[35] There was no significant difference in treatment toxicity between treatment and control group, or between HIV positive or negative patients. Adverse events attributed to mEHT were minor (adipose and surface burns) and did not affect compliance with treatment. At 6 weeks, mean change in cognitive function was significantly better in the hyperthermia group, and at the 3-month mark, post-treatment fatigue and pain were significantly better in the intervention group ($p < 0.05$). Compared to control, there was a significant improvement in the HT group for social functioning ($p = 0.049$) and emotional functioning ($p = 0.017$) at 3 months. The third publication included a sub-analysis to evaluate the abscopal effect in a subgroup of 108 patients who had involved lymph nodes outside of the treatment field and had an evaluation at 6 months.[14] Participants in the HT arm experienced significantly higher complete metabolic response (complete response on F-FDG PET/CT scan), a marker for the abscopal effect, compared to control (24.1% vs 5.6%, $p = 0.013$). Finally, the most recent publication presented results of 2 and 3-year overall and disease-free survival, QOL, toxicity, and cost-effectiveness.[37] The addition of mEHT to CRT resulted in significantly better 2 and 3-year DFS (36.4% vs 13.7%, $p < 0.0001$; and 35.4% vs 13,7%, $p < 0.0001$ respectively), but did not significantly improve OS. There were no significant differences in late toxicity between groups. Several EORTC subscales and symptoms were significantly better in the mEHT arm compared to control arm at 2 years, including pain ($p = 0.037$), cognitive function ($p = 0.004$), and role functioning ($p = 0.018$). Finally, mEHT was determined to be cost effective over a 3-year period primarily due to decreasing recurrences and progression which are costly. The probability that mEHT added to CRT decreases costs are 82% in a publicly funded model and 78% in a privately funded model.[37] The incremental costs for CRT only were estimated to be 36,836.65 and 37,422.82, South African Rand (ZAR) for the publicly funded and privately funded models respectively.

Lastly a controlled clinical trial was published in 2017 evaluating HT alongside chemotherapy in patients with recurrent cervical cancer.[34] The quality of the trial is questionable in certain respects. It is not clear if participants were randomized to their treatment allocation or not and the presentation of the results in some places appears incomplete. Patients with recurrent cervical cancer who were previously irradiated received either platinum-based chemotherapy plus mEHT (n = 18) or chemotherapy alone (n = 20). mEHT was administered 3 times weekly for the duration of chemotherapy (36 sessions total). The study found that the objective response rate was superior in the combined treatment group compared to the control group (p = 0.046), however there was no significant difference in overall survival between groups. Adverse events related to hyperthermia included a sensation of heat and abdominal discomfort reported in 44%. Although the study showed promise for this treatment combination for recurrent cervical cancer, the poor quality of the reporting makes judgment more challenging.

Several phase I and II studies have been conducted for HT and cervical cancer.[38-43] Given the availability of larger, higher quality studies (RCTs), these single-arm trials will only be discussed briefly. Three phase I/II studies evaluated HT administered simultaneously with Cisplatin in patients with pelvic recurrences of cervical cancer,[38,40,42] and one used a similar treatment but enrolled treatment naive patients.[41] The first study found that HT alongside six-weekly cisplatin treatments in 19 patients produced an overall response rate of 53% and no dose limiting toxicities.[38] Two patients developed subcutaneous burns and 11 treatments were stopped prior to 90 minutes due to discomfort, otherwise the treatment was well tolerated. The research team then enrolled an additional 28 people and analyzed the full dataset of 47 people in a separate publication.[42] They reported an objective response rate of 58% and a median overall survival of 8 months. In patients with pain, palliation through HT was achieved in 74% of participants. Toxicity was acceptable, and authors reported that response rates were slightly superior than expected with cisplatin alone. In a similar phase II study, LRHT was administered simultaneously with cisplatin for up to 12 treatments in 23 patients.[40] The response rate was 52%, median duration of response 9.5 months, mOS 8 months, and 1-yr survival 42%. Toxicity was moderate and mostly attributed to cisplatin. Subcutaneous fat necrosis occurred in 10% of cycles, 2 patients developed skin burns, and mild pain was reported in 15% of cycles. A similar treatment approach was used in a phase I/II study in patients with treatment-naive stage IIB-IVA cervical cancer; early [41] and late results [41] were published. The study enrolled 68 people who were treated with RT, weekly cisplatin, and four weekly whole pelvis HT treatments. After treatment, a complete response was achieved in 90% of patients. Two-year DFS and OS were 71.6% and 78.5% respectively, and 5-year DFS and OS were 57.5% and 66.1% respectively. The authors report that these results are within typically expected results for patients treated with standard of care.

One phase II study administered HT to 18 patients with advanced cervical cancer receiving 28-fractions of radiotherapy.[39] HT was administered twice each in week 1 and week 4. Thirteen patients had a complete response, 4 patients a partial response, and the local control rate was 48% at 2-years. The authors concluded that the combined treatment was feasible and

well tolerated, with toxicity being similar to radiation alone.

Colorectal & Anal Cancer

Evidence at A Glance:

Twelve single-arm trials in 13 reports[44-56] and seven observational studies[57-63] were identified involving patients with rectal cancer. One retrospective observational study[64] and two single-arm trials[65,66] included patients with mixed colorectal cancers. One observational study (n = 112)[67] included patients with anal cancer. HT may confer some benefit to response and survival for patients with rectal cancer undergoing neoadjuvant chemoradiotherapy (CRT), however, more rigorous trials are warranted. The benefit of HT use for rectal cancer outside of the perioperative setting is not as well defined. HT may be an option for pain relief in patients with colorectal cancer. Research is limited for the use of HT in patients with anal cancer.

Rectal cancer:

Twelve single-arm trials in 13 reports [44-56] and seven observational studies[57-63] were identified involving patients with rectal cancer. All administered HT alongside CRT, and all but one study[47] administered treatment pre-operatively. Overall, the addition of HT to standard care may confer treatment response and survival benefits for patients diagnosed specifically with rectal cancer undergoing perioperative CRT. However, as no RCTs were identified, future rigorous studies are required to make conclusions regarding true magnitude of effect.

Chemotherapy agents included in the 12 single arms trials were capecitabine or 5FU, with or without oxaliplatin. HT was administered 1-2 times weekly during CRT. Studies ranged in size from 20-105 participants. Studies evaluated heterogeneous endpoints, and synthesis is challenging, however the most common endpoints are summarized below. Response rates were assessed in several studies, using various techniques. Complete pathological responses ranged from 0-19.6% in six studies.[53] The Dworak regression system was used to evaluate response rates in several studies. Tumor regression grades (TRG) of 4 (complete response) were found in 22%[54] and 29.8%[45] of participants in two studies, and three studies reported TRG of 3 + 4 (near complete and complete response) to be 50%[56], 52%[55], and 76.7%[46,49]. Other studies reported on tumor downstaging, which was achieved in 41-65% of participants.[46] Survival outcomes were reported in several studies, again due to various methods of reporting, summarizing the data is difficult. In studies that reported on 5-year OS, results ranged from 29%-95%,[49] however it should be noted that the 29% was a low outlier,[56] with other studies ranging from 73.5-94%. One study each reported on 10-yr OS (55%),[54] 3-year OS (94%),[44,47,48,50,51,56] 30-month OS (85% for primary rectal cancer and 60% for recurrent),[51] and 2-year OS (91%).[45] Recurrence or disease-free survival was reported at 5-years to be 54.8%,[47,48,51] 77%,[55] and 74.5%.[46] Finally, two studies noted that patients with higher tumor temperatures achieved better outcomes.[50] Studies generally reported that the treatment was well tolerated, with adverse events including those expected such as local pain, discomfort, and skin or adipose burns. Drawing conclusions from single-arm trials, especially with significant heterogeneity in reporting is challenging. Overall, most studies reported that response rates and

survival outcomes were encouraging, thus warranting further study.

Seven observational studies were identified for rectal cancer; three were retrospective controlled,[57,59,62] one mixed retrospective and prospective controlled,[63] and 3 uncontrolled.[57,59] The four controlled observational studies all compared neoadjuvant CRT (5-FU or capecitabine) with or without HT in patients with rectal adenocarcinoma.[58,60,61] Three studies reported on survival outcomes, and none of them found significant improvement (including OS, DFS, or RFS) with the addition of HT.[57,62,63] In an observational study by Kim et al (n = 120),[63] there was no significant improvement in tumor downstaging (80.7% vs 62.7%, p = 0.09), or tumor regression rates between groups, however patients with large tumors had a significantly higher rate of tumor regression compared to controls (31.6% vs 0%, p = 0.024). In a study by Wang et al (n = 150)[62] there was greater T-downstaging at surgery in the HT group compared to controls (82% vs. 62.7%; p = 0.016). This effect was more pronounced in patients with an elevated neutrophil to lymphocyte ratio (NLR) (OR 3.324; 95% CI 1.262–8.751; p = 0.015). A third study reported that while sphincter preservation therapy occurred in 66% of HT patients and 64% in controls,[59] for those who received at least 4 HT treatments the complete response rate was significantly better than control (22.5% vs 6.7% respectively; p = 0.043). Overall, the results were mixed with no strong evidence of benefit with the addition of HT.

A mixed retro/prospective uncontrolled study included patients with rectal adenocarcinoma (stage I-IV) who received HT post radiation, while receiving capecitabine, with the majority (n = 33) undergoing surgery after treatment completion.[60] Local control rate was 18.5%, with 75% of tumor specimens downgraded from T2 to T0. No major adverse events occurred, with only once case of perianal dermatitis. One uncontrolled retrospective observational study (n = 93) reported downstaging of tumor size (according to TNM staging) scores in 45.2% of participants and lymph node scores (according to TNM staging) in 58.1%.[61] Pathological response was observed in 21.5% of patients, with 100% of participants having negative distal resection margins, with 84 participants still alive at a median follow up of 37 months. Lastly, a small (n = 14) retrospective observational study which included patients with local recurrence of rectal cancer, receiving HT, radiation, and chemotherapy (5-FU) reported a complete remission rate of 38.5% and a partial remission rate of 15.3%.[58] Five participants experienced grade I-III skin reaction, with 5 reporting pain during HT.

Colorectal Cancer (Mixed)

One retrospective observational study[64] and two single-arm trials[65,66] included patients with mixed colorectal cancers. Compared to studies looking specifically at patients with rectal cancer, there is limited information regarding the efficacy of HT for those with colorectal cancer. As all three identified studies focused primarily on QOL and symptom management, no comment can be made regarding survival at this time.

One uncontrolled observational study retrospectively evaluated patients with recurrent unresectable colorectal cancer who received HT and radiation (a subset of 6 patients also received chemotherapy) for pain management.[64] Complete pain resolution rate was 22%, with 37% having “good” pain relief, and 15% no change. Median duration of pain relief

was 7 months. A single-arm trial included 10 patients with colorectal cancer who had unresectable and chemotherapy-refractory liver metastases receiving radiation and HT.[65] Four of ten participants experienced partial pain relief, with no change noted at the 3-month timepoint, and 3/10 participants experienced partial liver metastases response. Compared to baseline, no significant QOL changes were noted at 3 months, with local progression-free survival being 30%. A second single arm trial (n = 72)[66] enrolled patients with a history of colorectal cancer who experienced either pelvic recurrence or had unresectable tumors. The combination of radiation and HT produced "good palliation" in 75% of participants, with 15% experiencing objective remission. Median survival was 11 months, with 17% of participants alive at 3-years.

Anal Cancer

There is insufficient evidence to comment on the efficacy of HT for patients with anal cancer, as only one observational study was identified.

One observational study (n = 112)[67] included patients with stage I-IV anal cancer, receiving chemotherapy (5-FU + Mitomycin C) and radiation, with or without HT. The HT group experienced significantly better 5-year overall survival compared to controls (95.8% vs 74.5%, respectively, p = 0.045) and 5-year disease-free survival (89.1% vs 70.4%, p = 0.027). No significant differences were noted for disease-specific survival, regional failure-free survival, or distant metastasis-free survival. Hematotoxicity and telangiectasia were significantly higher in the HT group (p=0.032 and p = 0.009, respectively).

Esophageal Cancer

Evidence at A Glance:

One meta-analysis of 19 RCTs,[68] two single-arm trials,[69,70] and one observational trial[71] have been published for esophageal cancer and HT. Results are suggestive of benefits in response rate and survival outcomes when combined with neoadjuvant conventional care, with a good safety profile. Although results were consistent across studies, the quality of the RCTs was generally low.

A systematic review and meta-analysis of 19 RCTs (n = 1519) for HT and esophageal cancer was published in 2017.[68] The paper compared the effect of combined HT and chemoradiotherapy (HCRT) to either chemoradiotherapy (CRT) or radiotherapy (RT). Compared to CRT, HCRT significantly improved 1-year survival rates (OR 1.79, 95% CI 1.12-2.84, p = 0.01). HCRT also significantly improved 3-, 5-, and 7-year survival outcomes; however, there was no statistically significant difference for 2-year survival. HCRT significantly improved the response rate to treatment compared to CRT alone (OR 2.00, 95% CI 1.49-2.69, p < 0.00001), but did not significantly alter the recurrence rate, or distant metastasis rate. HCRT decreased several adverse effects of CRT including gastrointestinal reactions, leukocytopenia, and radiation esophagitis (OR 0.43, 0.49, and 0.43 respectively, all p < 0.0001). The authors suggested that the reason for the reduced toxicity with the inclusion of HT may be its ability to reduce the dose of CRT due to synergy. When comparing HCRT to RT, HCRT significantly improved 1-year survival (OR 3.2, 95% CI 2.07 – 4.95, p < 0.00001), as well as survival at 2 (OR 2.09, 95% CI 1.13- 3.85, P = 0.02), 3 (OR 2.43, 95% CI 1.67, 3.51, P < 0.00001), and 5 (OR 3.47, 95%

CI 1.08, 11.17, P = 0.04) years. There were fewer recurrences and distant metastases in the HCRT group, and superior rates of complete response. Rates of several adverse reactions trended toward the HCRT group, including gastrointestinal reaction, leukocytopenia and radiation esophagitis, however the differences were not statistically significant. This is not unexpected given that many of the AEs are anticipated with the addition of chemotherapy, and thus it is unlikely the HT was the cause. Only three of the studies were published in English and could be reviewed further.[72-74] In these three studies, HT was administered twice weekly on the same day as radiotherapy (either simultaneous to or immediately prior), and all studies applied the therapies as neoadjuvant treatment before surgery. When taken together these results demonstrate efficacy for esophageal cancer; however, it should be noted that the quality of the individual RCTs was generally low. Further well designed RCTs are warranted to confirm these results.

In addition to the meta-analysis, two single-arm studies[69,70] and one observational study[71] were reviewed. A phase I-II study evaluated feasibility and toxicity of combined chemotherapy and HT for patients with esophageal cancer (primarily T3N1).[70] LRHT administered on day 1 of a 21-day cycle of neoadjuvant cisplatin + etoposide was feasible and had acceptable toxicity. Twenty-two of 26 patients who received at least one treatment underwent surgery. There were no post-operative complications attributed to neoadjuvant HT and chemotherapy. A phase II study enrolled 28 people with resectable esophageal cancer who were treated with neoadjuvant chemoradiation with HT.[69] Patients received daily radiation and once weekly chemotherapy (paclitaxel-carboplatin) and HT, for 5 weeks. Twenty-five of the 28 patients completed the 5-weeks of treatment, 26 patients underwent surgery, and all had resections with clear margins (R0). Response rate was 74%, with 19% having a complete pathological response. After a median follow-up of 37 months, the locoregional control of disease was 100%, 1-year, 2-year and 3-year survival were 79%, 57%, 54% respectively. Mild physical discomfort during HT was the most common reported adverse effect. The addition of HT was deemed feasible and demonstrated promising results and acceptable toxicity by study authors. One retrospective observational study combined intensity modulated radiotherapy (IMRT) with twice weekly supraclavicular HT to patients with upper and middle esophageal SCC with supraclavicular lymph node metastasis.[71] Most patients (88%) also received chemotherapy with cisplatin. The 3-year PFS and OS was 34.9% and 42.5% respectively, toxicity was low, and the authors recommended a clinical trial to further evaluate HT in this population.

Gastric Cancer

Evidence at A Glance:

Three RCTs,[75-77] one single-arm study,[78] and two observational studies[79,80] were identified. HT is a promising treatment to improve survival in advanced gastric cancer and as a neoadjuvant treatment for operable gastric cancer. Future rigorous trials are warranted to further explore the effect of HT in this population.

Two RCTs evaluated HT in patients with advanced gastric cancer. In the first, the addition of

regional HT to chemotherapy (CT) improved the disease control rate and median survival compared to chemotherapy alone in a phase II RCT (n = 118).[75] Participants received chemotherapy (oral S-1 and IV oxaliplatin on day 1 of a 21-day cycle), with or without HT twice weekly. For the HT+ CT group compared to the CT only group, the disease control rate was 70.9% vs 46.0% (p = 0.006), mOS was 23.5 months vs 14 months (p = 0.01), and the 3-year survival rate was 11.4% vs 0% (p = 0.018), respectively. There was no difference in grade 3/4 AEs between groups. The second RCT, presented in abstract form only, randomized 60 patients to HT plus radiotherapy (RT) (n = 30) or RT alone (n = 30).[77] There were significantly higher effective and local control rates in the HT+RT versus RT alone (63.33% vs. 33.33%; P = 0.020 and 93.33% vs. 73.33%; P = 0.038, respectively). Similarly, OS at 1, 2, and 3 years was significantly higher in the HT+RT group versus RT alone group (72.7%, 38.1%, and 10.4% vs. 51.9%, 17.3%, and 3.5% respectively, P < 0.05). The patients in the HT+RT group had a prolonged median OS (15 vs. 13 months, P = 0.04) and progression-free survival (11 vs. 9 months, P = 0.03) compared to the RT alone group. The incidence of vomiting was significantly lower in HT+RT (76.67%) versus RT alone (90%, P = 0.047), otherwise there were no significant differences in adverse reactions between groups.

One three-armed RCT (n = 293) included patients with newly diagnosed non-metastatic gastric cancer who were randomized to surgery alone, preoperative radiation (RT), or preoperative RT plus HT (RTHT).[76] Compared to surgery alone, RTHT significantly improved 3-year survival (57.6% ± 6.3 vs 35.5% ± 4.9, p < 0.05) and 5-year survival (51.4% ± 6.6 vs 30.1 % ± 4.7), p < 0.05). RT alone did not significantly improve survival compared to surgery alone although trended towards benefit (51.8% ± 6.8 vs 35.5% ± 4.9 for 3-year and 44.7% ± 7.1 vs 30.1% ± 4.7 for 5-year survival, p > 0.05). There was no significant difference between survival for the RT group compared to RTHT group. However, RTHT showed slight trends for improved survival by increasing the 3 and 5 years survival by 5.8% and 6.6% in comparison to preoperative RT alone.[76]

A small single-arm study evaluated HT in 25 patients with unresectable, recurrent gastric cancer.[78] The paper is a short communication and several key pieces of information are missing or incomplete, including participants' prior or concurrent treatments, methods, and objectives; thus little can be determined from this paper. Amongst the 9 patients who had peritoneal carcinomatosis who were treated with 1-3 times weekly HT, the survival outcomes were superior to a historical comparator (12.8 ± 8.6 months vs 6.4 ± 5.0 months, p < 0.01), and performance status was maintained in those who had ≥ 15 HT treatments compared to those who received fewer. Finally, two retrospective studies evaluated HT in different gastric cancer populations. In one, regional abdominal HT was administered during intraperitoneal (IP) cisplatin treatment for patients with stage IIA-IIIC surgically resected gastric cancer.[79] Patients received 3 to 6 cycles of IV 5FU and leucovorin (days 1-5), IP cisplatin (day 1), and HT (day 1). After 58-months follow up, 68.2% experienced a recurrence and 45.5% had died. The authors noted that this produced a better local recurrence control that typically expected and that it may reduce peritoneal metastasis, however more research is needed. The second retrospective study evaluated a multimodal intervention of chemotherapy (docetaxel, carboplatin, 5FU), ketogenic diet, insulin

induced hypoglycemia, hyperbaric oxygen therapy (HBOT), and mEHT in patients with stage III/IV gastric cancer.[80] The treatment was administered in a 3-week cycle of chemotherapy (days 1 and 8), with HT and HBOT given sequentially for 60 minutes each on the day of, or day after, chemotherapy. The complete response rate was 88%, mean overall survival 39.5 months (95% CI 28.1-51.0), and mean progression free survival 36.5 months (95% CI 25.7-47.2). There were no adverse events attributed to the ketogenic diet, mEHT, or HBOT. The authors state that compared to other studies in this population, the survival outcomes were superior, and more research is warranted.

Head and Neck Cancer

Evidence at A Glance:

One systematic review and meta-analysis of 6 controlled trials,[81] one non-randomized controlled trial,[82] five single-arm clinical trials, [83-87] and three observational studies[88-90] were identified. Combined with radiotherapy, hyperthermia may improve response rates in patients with locally advanced disease based on controlled trials, and further research is warranted for combination with CRT.

A 2016 systematic review and meta-analysis of HT with radiotherapy for primarily locally-advanced head and neck cancer (HNC) reviewed six controlled studies (five randomized).[81] One study used intracavitary hyperthermia which is outside the scope of this monograph, however, the results were presented together, and it does not appear that the findings would significantly skew the overall findings. The complete response rate of RT alone was 39.6% compared to 62.5% with HTRT (OR 2.92, 95% CI 1.58 - 5.42, p = 0.001). The risk difference was 0.25 (95% CI 0.12 – 0.39, p < 0.0001). Funnel plots did not detect any publication bias, however, there were a small number of studies included. No study reported any significant increase in toxicity with HTRT compared to RT alone; rates of grade III/IV toxicities were similar between groups. Collectively, HT combined with RT appears to increase the likelihood of a complete response to treatment by about 25% in patients with locally advanced HNC.

Two single-arm studies evaluated HT with radiation for head and neck malignancies. A phase I-II study delivered HT (2-6 treatments) and hyperfractionated radiotherapy to 27 patients with HNC squamous cell carcinoma (SCC) with cervical lymph node metastasis.[83] The overall response rate was 92% (CR in 77%, PR in 15%). The 5-year nodal control and survival were 64.5% ± 19%, and 24% ± 10% respectively. The treatment was generally well tolerated; acute cutaneous skin effects were moderate, one patient developed a cutaneous ulcer, there were no thermal blisters, and 12 patients reported local discomfort treated with NSAIDs. A phase I/II single-arm trial[84] included 13 participants with parotid cancer (20 lesions total) and administered HTRT (30 minute sessions at a target temperature of 42 C^{o}). 16/20 lesions treated with combination therapy showed complete response, with the remaining 4/20 partial response. Three participants experienced treatment failure at 13, 14 and 36 months. Three cases of grade IV necrosis were reported, and one participant refused to continue HT treatment after one session.

Three single-arm trials and one observational trial evaluated the combination of HT and chemoradiotherapy for HNC.[85,86,88,91] All three studies

administered the same basic treatment regimen: radiation 5 times per week with weekly cisplatin and twice weekly HT. In one study, 53 patients with previously untreated HNC with N2 or N3 metastatic cervical LNs were treated with the tri-modal regimen, with up to 8 HT treatments.[85] One month following treatment, the local complete response rate was 82% and partial response rate 9%; the nodal complete response rate was 85% and partial response rate 9%. At 2-years, the overall survival and disease-free survival were 51 ± 9% and 54 ± 8%. Treatment toxicity was deemed acceptable. In the second study, 20 patients with recurrent metastatic cervical lymph nodes (LNs) following prior surgery with or without radiation were treated.[86] Symptom palliation (pain, bleeding, difficulty breathing, difficulty swallowing, difficulty speaking) was achieved in 19/20 patients. Response rates were 8/20 for complete response and 11/21 for partial response. The 1-year OS was 39% ± 11%, and 3-patients were alive at 3-years. Adverse events were generally grade 1-2, and included acute skin toxicity and haematological toxicity, 1 patient each experienced grade 3 skin and haematological toxicity. A retrospective analysis of 40 patients with advanced HNC treated with 7-weeks of radiation, weekly cisplatin or paclitaxel, and weekly HT found the combination to be feasible and encouraging for response.[88] Of 38 evaluable patients, the complete and partial response rates were 76.23% and 23.68% respectively, and 1-year and 2-year OS were 75.69% and 63.08% respectively. The authors noted that the mucosal and thermal toxicities were not more severe than expected with chemo-radiation treatment.

Three small studies evaluated HT with chemotherapy alone.[82,87,90] A non-randomized controlled clinical trial explored the use of HT with two different chemotherapy regimens for patients with neck node metastases resulting from HNC.[82] Participants either received Adriamycin alone, bleomycin alone or one of these two chemotherapeutic agents in combination with HT. HT was delivered every other day, for 45 minutes, for a total of 10 sessions, occurring 3-4 hours after the first chemotherapy injection. In the control group the overall tumor response rate was 36%, compared to 100% in the intervention group (no statistical analysis conducted). In a pilot study, 8 patients with advanced (N2 or N3 neck adenopathy) or recurrent squamous cell carcinoma (SCC) of the head and neck were treated with carboplatin chemotherapy plus simultaneous HT, once every 4 weeks for 1-3 rounds.[87] There was one CR and 2 PRs. Six patients died within 4-13 months, and there were 2 long-term survivors who went on to receive radiation, and in one case surgery. Treatments were well tolerated. HT with chemotherapy may be an effective treatment for local SCC of the lip based on results from 31 patients treated with twice weekly IV bleomycin and methotrexate followed by microwave hyperthermia for 4.5-7.5 weeks.90 The complete response rate was 93.55% and partial response rate was 6.45%. Among those with a complete response, during a 5-year follow-up there was one local recurrence and one death. The authors noted that the cosmetic results were good, the treatment was well tolerated, and that this combination could be an effective option for those for whom surgery or radiation is not possible or may not have acceptable cosmetic outcomes.

Lastly, a small retrospective analysis evaluated HT with radiation and cetuximab.[89] Six patients with locally advanced SCC were treated with radiation for 6-7 weeks, with once weekly cetuximab and HT. All patients experienced a complete response, side effects

were mucositis and acneiform rash in all patients. The authors determined this combination was feasible and encouraging.

Hepatobiliary Cancer

Evidence at A Glance:

Two single arm trials[92,93] and one observational study[94] in liver cancer, and one single-arm study of biliary cancer were identified.[95] There is insufficient data to comment on the efficacy of HT for outcomes in patients with hepatobiliary cancers, although preliminary data is sufficient to warrant further research.

One study investigated the use of HT combined with hepatic arterial embolization and degradable starch microspheres for 26 patients with liver cancer (20 primary, 6 metastatic).[92] Local tumor response >50% was obtained in 40% of evaluable participants with primary liver cancer (4/10). Based on 17 participants with primary liver cancer, 14/17 experienced tumor marker (alpha-fetoprotein) level decreases within 1-5 weeks post treatment. One case of pain was reported due to overheating. Authors noted that results were promising, and further study warranted. A second trial included a larger variety of patients, including those with hepatocellular carcinoma (n = 30), hepatic cholangiocarcinoma (n = 5) or metastatic liver carcinoma (n = 22) receiving a combination of HT and transcatheter arterial chemoembolization.[93] Treatment resulted in an overall response rate of 21.1%, and in those who achieved a tumor temperature of 42°C or more, a response rate of 40%.

An observational study (n = 68) of patients receiving surgery divided participants into four groups: lobectomy alone (n = 14), lobectomy + HT (n = 12), regional hepatectomy alone (n = 16), or regional hepatectomy + HT.[94] All patients received post-operative chemotherapy (5-FU). Both in the lobectomy groups and the hepatectomy groups, those who received additional HT experienced significantly longer mean survival (345.5 days vs 432.6 days, p = 0.01, and 525.4 days vs 402 days, p = 0.009, respectively). No significant differences between groups were noted regarding pathological assessment of margins post interventions.

One small (n = 8) single-arm clinical trial evaluated the effect of HT with CRT for patients with advanced extrahepatic bile duct cancer experiencing obstructive jaundice.[95] Patients were treated with radiation with once weekly chemotherapy (5FU + cisplatin or methotrexate) simultaneously with HT immediately following radiation. After 2-8 HT treatments, the response rate (CR + PR) was 63%, and the mean survival was 13.2 months $\pm$ 10.8 months. The authors stated that the results were promising for local control and survival.

Hodgkin's Lymphoma/Disease

Evidence at a Glance:

There is insufficient evidence to comment on the efficacy of HT for patients with Hodgkin's lymphoma, as only one single-arm trial was identified.

One single-arm trial explored the effect of a combination of radiation and HT for patients with Hodgkin's lymphoma experiencing superficial

recurrence.[96] HT (1-4 sessions) delivered immediately after radiation for 45 minutes resulted in all participants experiencing partial response (>50% tumor volume reduction). Participants tolerated hyperthermia well. No treatment limiting pain, burns or blisters occurred. Mild-moderate discomfort was the most common side effect, and most experienced painless/asymptomatic fibrosis of the treatment area.

Lung Cancer

Evidence at A Glance:

Fourteen studies of HT and lung cancer were included; four RCTs,[97-100] three single arm-clinical trials, [101-103] and seven observational studies.[104-110] Based on higher quality evidence, HT's ability to improve survival, response and/or progression appears limited when added to chemotherapy and radiation regimens, except possibly in the scenario where only supportive care is available.

A phase II randomized controlled, single-blinded, clinical trial (n = 80) explored response and progression endpoints in patients with stage IIIB-IV non small cell lung cancer, (NSCLC) receiving gemcitabine and cisplatin with or without the addition of HT.[97] No significant differences were observed regarding response rate between groups. Furthermore, no significant differences were noted between groups for complete remission, partial remission, stable disease, or disease progression ($p > 0.05$). QOL was also explored, using the Clinical Benefit Response (CBR) tool. The overall score was significantly improved compared to baseline in the HT group (82.5%) compared to control (47.5%) ($p < 0.05$). Various individual components of QOL, however, were not significantly different between groups.[97]

A RCT including patients with locally-advanced NSCLC found that the combination of HT and radiation therapy significantly improved progression free survival, but not overall survival at 1 year compared to radiation alone.[98] The 1-year local PFS in the intervention group was 67.5% compared to 29.0% in control ($p = 0.036$), and 1-year overall survival was 43% in the intervention group compared to 38.1% in the control group ($p = 0.868$). Acute toxicities were generally mild and not significantly different between groups ($p = 0.58$).[98]

Two studies evaluated the combination mEHT with intravenous vitamin C (IVC) in patients with advanced lung cancer receiving supporting care. In a small phase I trial, 15 patients with stage III/IV NSCLC who had failed previous treatment either received IVC (1-1.5g/kg) after HT, both simultaneously, or IVC before HT.[99] Treatment was administered 3x/week over 4 weeks. The objectives included safety, tolerability, pharmacokinetics of IVC and QOL with the EORTC-QLQ-C30. The study found that the peak ascorbic acid concentration was significantly higher when mEHT was administered simultaneous to IVC. They found the combined administration to be safe and well tolerated with minimal and mild side effects. For QOL, there were significant improvements from baseline to 4-weeks for the physical functioning scale, and the following side effects were significantly improved: fatigue, dyspnea, insomnia, appetite, diarrhea, and financial problems. The same study group conducted an RCT, which found that the combination of IVC and HT in patients with refractory NSCLC (stage IIIb-IV), in addition to basic supportive care, improved survival, progression and QOL compared to supportive care alone.[100] Over the course of approximately eight weeks (3 treatments/week), participants in the intervention group

received 1g/kg IVC and concurrent HT for 60 minutes, covering the entire lung alongside basic supportive care. Median OS in the treatment group was 9.4 months compared to 5.6 months in control (HR 0.33; 95% CI 0.16-0.41) ($p < 0.0001$).[100] Median progression free survival was 3 months in the treatment group compared to 1.85 months in the control (HR 0.33; 95% CI: 0.12-0.32) ($p < 0.0001$). The three-month disease control rate was 42.9% in the treatment group compared to 16.7% in the control group ($p = 0.0073$). Significant QOL improvements in the treatment group were noted for physical, emotional, and global measures compared to control, with significant symptom improvements also noted for fatigue, pain, nausea, SOB, and appetite loss. No significant changes were noted for biomarkers.

Three single-arm trials explored the use of HT in patients with lung cancer, one combining it with second-line docetaxel[101] and two combined with radiotherapy compared to historical controls.[102,103] In patients (n = 29) receiving second-line docetaxel and radiofrequency HT for inoperable locally advanced NSCLC, treatment was safe and well tolerated, and the response rates were encouraging.[101] Patients received up to 4 cycles of docetaxel and up to 32 HT treatments administered twice weekly. There were no treatment discontinuations due to hyperthermia-toxicity. Median PFS was 4 months (range 0-13), 1-year PFS rate was 10.3%, overall response rate: 25.9%, tumor control rate 66.6% (CR + PR + SD), mOS 11 months (2-18+) and 1-year OS rate 44.8%. Two studies used historical controls to assess the effects of HT combined with radiotherapy. One of the trials compared patients with direct bony invasion from NSCLC receiving radiation therapy with HT to 13 historical controls.[102] The participants received 6-7 weeks of radiation with HT immediately following (2-4 weekly sessions). In the treatment group, 10/13 patients responded to treatment compared to 7/13 in the historical control group (not statistically significant). The 2-year local recurrence free survival and overall survival in patients without distant metastases was superior in the HT arm compared to the comparator group, but the results were not significant (76.1% vs 16.9%, $p = 0.19$: 44.4% vs 15.4%, $p = 0.30$, respectively). There were no grade 3 or 4 pulmonary complications in either group. The second study enrolled 19 patients with stage IIIA-IIIB NSCLC receiving a combination of HT and radiotherapy, comparing results to 26 historical controls.[103] In this study, both complete response rate ($p < 0.005$) and overall response rate ($p < 0.05$) were significantly better in the treatment arm compared to historical controls. Overall, 3-year local relapse-free survival and overall survival rate were found to be significantly better in the HT combination group ($p < 0.01$ for both).

Two retrospective studies evaluated HT with RT for NSCLC. One included 33 patients with recurrent NSCLC receiving a median of 5 HT treatments immediately after radiation.[104] The objective response rate was 42%, mOS was 18.1 months, and local control was 12.1 months. Three patients experienced thermal burns which resolved with conservative treatment, and toxicity was considered acceptable by investigators. In the other, 35 patients with stage III NSCLC who received HT with radiotherapy were included with an objective of assessing the effect of different power outputs.[105] Using a 8-MHz RF-capacitive system, a medium output of $\geq$ 1200 W was found to be a significant prognostic factor for overall survival ($p = 0.01$), local recurrence-free survival ($p = 0.004$) and distant metastasis-free survival ($p = 0.02$). The median overall survival, local recurrence-

free survival, and distant metastasis-free survival times were 14.1, 7.7, and 6.1 months, respectively.

A retrospective case-control study evaluated changes in cancer-related pain in patients with NSCLC (44% stage IV) who received at least 2 external RHT treatments while receiving standard care.[106] Pain was measured using the Effective Analgesic Score (EAS) which includes pain medication use and subjective pain. Pain measures were taken at four time points: baseline (days 30 to 0), time 1 (days 1 to 60), time 2 (days 61 to 120), and time 3 (days 121 to 180) Thirty-two patients were included in the HT arm, and 83 were selected as matched controls. The median number of HT treatments was 19. There was a significant increase in EAS in the HT-arm for time point 1 compared to control (mean difference: 101.76 points, 95% CI 10.2-193.32, p = 0.03), indicating increased pain in the HT arm. There was a non-significant decrease in pain at time point 3 in the HT arm compared to the control arm. The authors hypothesized that the initial increase in pain may have been due to direct thermal damage.

Outside of NSCLC, one retrospective study evaluated HT for malignant mesothelioma, and another for superior sulcus tumors (Pancoast tumors). A retrospective chart review of patients with malignant mesothelioma of the pleura from 1979-1996 looked at factors influencing the outcome of palliative radiotherapy on pain management, response rate, and survival.[107] Twenty-one patients received local HT (median of 4 treatments) with RT, and their data was compared to 24 controls. The authors noted that there appeared to be improvements in pain control and duration, and tumour responses in the HT group, however, no statistical analysis was conducted. Of note, the rates of CR were 4 vs 2, and PR were 13 vs 5 for HT and control groups respectively. The findings are interesting but require further research given the methodological limitations. A retrospective case series evaluated the combination of RT plus HT with or without chemotherapy for 24 patients with superior sulcus tumors (Pancoast tumors).[108] Patients were treated with radiation plus 1-2 weekly HT treatments, and approximately half also received chemotherapy. The 3-year OS, local control, and distant-metastasis free survival rates were 47%, 55%, and 71% respectively. Toxicities were mild (grade 1 and 2), other than one case of grade 3 dermatitis. The authors noted the treatment approach was feasible and promising and encouraged additional research.

Two retrospective studies investigated the use of unique combination treatments which include HT, conventional care, and the addition of other non-standard treatments. A retrospective study evaluated a multimodal intervention of chemotherapy (carboplatin + paclitaxel), ketogenic diet, insulin-induced hypoglycemia, hyperbaric oxygen therapy (HBOT), and mEHT.[109] Patients with stage IV metastatic lung cancer were treated with eight, three-week cycles of chemotherapy, with mEHT and HBOT given sequentially for 60 minutes each the day of or day after chemotherapy. The response rate was 61.4%, mean overall survival 42.9 months (95% CI 34.0-51.8), and mean progression free survival 41 months (95% CI 31.1-50.9). There were no adverse events attributed to the ketogenic diet, HT, or HBOT. The authors state that compared to studies using only carboplatin/paclitaxel in similar populations, the response rates and survival outcomes were superior, and more research is warranted. The second retrospective case series evaluated the combination of chemotherapy, HT, and HBOT, and reported it to be safe and feasible.

[110] Twenty-two patients with multiple pulmonary metastasis were treated with carboplatin-paclitaxel with simultaneous HT, and in 73% of patients HBOT immediately following. Treatment toxicities were mostly mild, and HT was well tolerated. The objective response rate was 65% and mOS was 17-months. The objective response rate was higher in those who received HBOT, however statistical significance was not calculated.

Melanoma

Evidence at A Glance:

Two RCTs[111,112], 3 single-arm trials[113-115], and a non-randomized trial[116] were reviewed. The addition of HT to standard care for melanoma may improve recurrence rates and tumor control, particularly for lesions treated with HT and RT.

Radiation followed by HT for patients with recurrent or metastatic melanoma lesions significantly improved the rate of complete response and local control compared to radiation alone in an RCT.[112] The study randomized 70 patients (134 lesions) to 3 fractions of RT alone, or RT followed by 60 minutes of HT. After 3 months, significantly more patients in the combined treatment arm achieved a complete response (62% vs 35%, $p < 0.05$). The 2-year local tumor control was 46% in the combined arm vs 28% in the control arm ($p = 0.008$), which resulted in an odds ratio for local control at 2 years of 1.73 (95% CI 1.07-2.78, $p = 0.023$). The dose of radiation and the size of the tumor were also prognostic variables.

A small RCT (n = 18) evaluated the impact of HT prior to intratumoral injection of dendritic cells (DC) in people with metastatic melanoma.[111] Patients were randomized to HT + DC injection 3 times in one week of a 28-day cycle (n = 9), or DC injections alone (n = 9). After the first 28-day cycle, the disease control rate was superior in the HT + DC arm compared to the DC arm (77.8% vs 44.4%, $p < 0.05$). Time to progression was significantly better in the HT + DC arm compared to the DC arm (5 months vs 2 months, $p < 0.05$), however there was no significant difference in median OS (13 vs 6 months, $p > 0.05$). Exact P values were not provided. There were more AEs in the combined treatment arm, however most were minor and resolved within 48 hours of treatment. Cellular assays demonstrated possible anti-tumor immune effects of the HT, including induction of cytotoxic T lymphoctyes, heat shock protein expression, and enhanced Th1/Th2 chemokine production.

HT combined with chemotherapy for recurrent or metastatic melanoma has been studied in a single-arm pilot study.[113] Thirty-two pre-treated patients were given once weekly HT with simultaneous cisplatin infusion for 4 weeks. Four-weeks post-treatment the objective response rate was 68.7%, the 1-year and 4-year actuarial survival rates were 68.7% 28.8% respectively. There were no serious local toxicities, mild and transient erythema was noted in most treatments. The authors considered the results satisfactory given the patient population.

Superficial or deep regional HT combined with CRT with carboplatin in patients with inoperable, metastatic melanoma resulted in a 34% complete response rate and 40% partial response respectively.[116] The small single-arm study of 15 patients found the treatment was well tolerated, however the mOS was 12 months which is not different from findings from others studies without hyperthermia.

Finally, two older studies evaluated HT with radiation for melanoma. One study included 92 patients with melanoma with a total of 181 lesions, of which 57 received both radiation and HT.[114] With radiation doses < 400 cGy, the addition of HT raised the complete response rate from 34% to 70%, and with doses > 400 cGy, the combination raised the rate from 63% to 77%. A similar single-arm trial combined HT with radiation for patients with metastatic melanoma, most of whom had been pretreated with various therapies.[115] Of thirty-four patients (a total of 84 treatment fields), a complete or partial response 3-weeks after treatment was achieved in 34/84 fields (40%), and local control was maintained in 31% of treatment fields after a mean follow-up of 14.6 months. Five patients remained alive after 36 months. The authors felt this combination warrants further study.

Ovarian Cancer

Evidence at a Glance: Seven reports of six single arm studies.[117-123] were identified. Although hyperthermic intraperitoneal chemotherapy (HIPEC) is often used in ovarian cancer, this technique is outside the scope of this monograph. At present, due to study heterogeneity and methodological deficits, no conclusions can be made regarding the use of LRHT in patients with ovarian cancer for survival or treatment response.

Three single arm studies combined HT with IVchemotherapy, all in advanced and pre-treated patients.[117-120] A phase I trial included 18 patients with platinum-resistant epithelial ovarian cancer, and investigated the effects of HT simultaneously given during dose-escalation cisplatin delivery.[117] Ten participants experienced a reduction in CA-125, however, only 2 experienced a sustained effect. At a median follow-up of 14 months, 7 patients remained alive. A similar phase I/II study looked at IV doxorubicin with whole abdomen HT for patients with refractory epithelial ovarian cancer, and published findings in two separate papers.[118,119] Patients (n = 30) were treated once every 4 weeks with IV doxorubicin followed by HT for 6 cycles or until disease progression or dose limiting toxicity occurred. The maximum tolerated dose (MTD) of HT was determined to be 90 minutes of power application or 60 minutes after an average vaginal or rectal temperature of 40°C was reached. The response rate was 10% (3 partial responses) and 27% had stable disease. The median time to progression was 3.3 months (95% CI 2.6-5.2), and median survival 10.8 months (95% CI: 8.8-17.4). Adverse events from HT occurred in 23% of patients and included grade 1-2 subcutaneous thermal injuries and skin burns.[118] Quality of life was measured, however only 10 patients completed all 6-cycles, and only 3 completed follow-up questionnaires, so not much can be determined. Overall QOL was above average at baseline and did not significantly change between baseline and cycles 4-6, possibly indicating some stability.[119] Lastly, a phase I/II trial enrolled 36 patients being treated with 2nd and 3rd line chemotherapy (most commonly liposomal doxorubicin, carboplatin, topotecan) and co-treated them with RHT[120]. The treatment was well tolerated; most toxicities were hematological. There was only one complete response (2.8%), 44% progressed, the mOS was 12 months. It is difficult to determine from single-arm trials such as these if there was clinical efficacy given that the majority of patients continued to progress, and the patients enrolled had advanced and refractory disease.

Abdominal HT was administered immediately after intraperitoneal (IP) chemotherapy in another two single arm studies.[121,122] The first study looked at feasibility and toxicity of IP carboplatin with abdominal HT in 13 patients with residual peritoneal disease following platinum chemotherapy.[121] Patients were treated with 1 cycle of IP carboplatin alone followed by 3 cycles of combined treatment. HT treatment was frequently discontinued early due to increased systemic temperature or adverse effects (abdominal pain, general distress, vomiting). Two patients were alive at 40 and 43 months, the target temperature for future studies was suggested to be 40°C. The study was published in 1996, and older technology may have been related to the poor tolerance. The second, and more recent study evaluated patients with advanced, recurrent, or progressive ovarian cancer treated with IP cisplatin with abdominal HT every 3-4 weeks for 6 cycles.[122] Among the forty-one patients in the phase I/II study, 44% had a response and the mOS was 30 months. HT was well tolerated and there were two instances of 2nd degree burns. The results were considered promising given that there were 10 patients who experienced a complete response.

One final study uniquely evaluated modulated electro-hyperthermia (mEHT) as monotherapy in patients with recurrent and refractory ovarian cancer who had either refused additional chemotherapy or for whom chemotherapy was not likely to have benefit.[123] The phase I/II study (n = 19) administered HT 2x/week for 3 weeks (considered 1 cycle) following a power escalation protocol up to 150W. Treatment was then continued for up to 6 cycles total. There were no DLT up to 150W. Although there was no control group, the findings for response rates, time to progression, and OS were not particularly impressive according to the researchers; after 3 and 6 cycles there was stable disease in 7/17 and 1/9 who were evaluable, respectively. The median time to progression was 4 months, and mOS was 8 months. Physical wellbeing as assessed by the FACT-O declined over the 6-cyle study period; social, emotional, and functional scores did not change. The treatment was reported to be well tolerated.

Pancreatic Cancer

Evidence at A Glance:

One phase II study[124] and 10 observational studies[125-134] for pancreatic cancer were identified. A systematic review of HT for pancreatic cancer was published in 2018, however, it combined locoregional HT, whole body HT, and intraoperative HT together.[135] While it is briefly described below, the data is not exclusively for LRHT. Overall, there is some preliminary data that the addition of HT to standard of care treatment in locally advanced or metastatic pancreatic cancer may improve objective response rates and median survival, however data from RCTs are needed.

The systematic review included a total of 14 studies (n= 395); 8 using regional HT (n = 189), 4 using intraoperative, and 2 using whole body.[135] None of the studies were RCTs, all were observational (eight retrospective), and six of the studies included a control group. The quality of studies was generally graded as poor. All patients had locally advanced or metastatic pancreatic cancer, and were treated with concomitant chemotherapy (60%), chemoradiotherapy (33%), or radiotherapy (7%). Data was not reported separately for the different types of HT, and thus the results must be interpreted with caution. There was evidence that the

addition of HT could improve outcomes for patients with advanced pancreatic cancer. The response rate across 11 studies was 33.3%, and for the 3 studies with control groups, it was 43.9% in the HT group compared to 35.5% in the control group. Overall survival was reported in 12 studies; the mOS was 10.5 months, and for 6 studies with a control group the mOS was 11.7 months for the HT group compared to 5.6 months for the control group. No statistical analysis was applied due to study heterogeneity. There were no serious adverse events related to regional hyperthermia, there was one case of subcutaneous fatty burn in a patient receiving intraoperative HT.

HT was evaluated alongside chemotherapy in patients with locally advanced or metastatic pancreatic cancer in five studies: one single-arm trial and four retrospective observational studies. A phase II study (n =18) evaluated gemcitabine chemotherapy with regional HT for patients with locally advanced or metastatic pancreatic cancer.[124] Patients received IV gemcitabine on days 1, 8, and 15 every 4 weeks, and once weekly HT the day before or after gemcitabine and continued until disease progression. The 1-year survival rate was 33%, mOS 8 months and 17.7 months for those with locally advanced disease, which the authors note is superior to gemcitabine monotherapy historically. The objective response rate was 11%, and disease control rate (OR + SD) was 61%. The treatment was well tolerated with HT-related AEs being mild, which included pain and skin rash.

The two most recent retrospective observational studies compared mEHT in addition to conventional care, to conventional care alone in patients with stage III-IV pancreatic cancer; both found statistically significant benefit to survival. One was a single-centre case-control study assessing OS and PFS in patients with inoperable stage III or IV pancreatic cancer (n=78).[133] OS weakly favoured the addition of mEHT ($p = 0.14$) and met statistical significance when case-control pairs were matched for age, sex and chemotherapy (median OS, $p = 0.03$). One-year OS ($p = 0.02$) and PFS ($p = 0.05$) were higher in patients treated with mEHT. There was no significant difference in survival between groups at year two or three. In a sub-group analysis there was no statistical difference in OS with mEHT based on the presence of metastasis. Patients with no ascites responded more to mEHT compared to those with ascites (HR advantage of mEHT: 0.52 95% CI 0.27-0.99, $p = 0.04$). Similarly, the other study[134] found significant improvements in the chemotherapy + mEHT group (n = 100) compared to the chemotherapy alone group (n = 58) for OS (19.5 months vs 11.02 months respectively, $p < 0.001$) and PFS (12 months vs 3 months respectively, $p < 0.001$). Toxicity and adverse events were comparable between the two groups.

HT was evaluated as an adjunct to low-dose FOLFIRINOX in a small retrospective study of 17 adults with advanced or metastatic pancreatic cancer.[125] Patients generally received HT once weekly, during chemotherapy administration. In a subset of 12 patients with metastatic disease given low-dose FOLFIRINOX as first line treatment with HT, the mOS was 17 months (95% CI 1.97-32.03). The authors note that this is better than published data without the addition of HT. The population was heterogenous, and better designed and controlled studies are needed. In patients with advanced or metastatic pancreatic cancer refractory to gemcitabine chemotherapy, regional HT has been used alongside second line gemcitabine + cisplatin and warrants further

investigation.[126] Twenty-three patients who were treated with second line gemcitabine (day 1), cisplatin (day 2 and 4), and regional HT (day 2 and 4) in a two-week cycle were retrospectively analyzed. HT was well tolerated, all AEs were mild (grade 1-2), and included discomfort because of bolus pressure (3%), power-related pain (7%), and position-related pain (17%). The disease control rate in those with CT-scans (n = 16) was 50%, the median time to progression was 4.3 months, median OS was 12.9 months, and the 6-month survival was 83%. This is a population that has poor outcomes, and the authors felt an RCT was warranted.

HT was studied alongside chemoradiotherapy (CRT) for locally advanced or metastatic pancreatic cancer in three observational trials, all of which found benefit.[127-129] A prospective cohort study (n = 60) found that the median overall survival was 15 months for those receiving twice weekly HT alongside CRT compared to 11 months in the CRT alone group (p = 0.025), and HT did not increase toxicity of CRT.[127] Despite a modest improvement in survival, the lack of randomization must be considered. A small retrospective analysis of patients receiving CRT or CRT with HT also found improved median overall survival in the combined treatment group.[128] Patients treated with once weekly HT in addition to radiation and weekly gemcitabine (n = 20), had a median overall survival of 18.6 months compared to 9.6 months for the 9-patients treated with only CRT (p = 0.01). A second small retrospective analysis (n = 13) compared regional HT with gemcitabine CRT to gemcitabine or 5-FU CRT alone for patients with locally advanced unresectable pancreatic cancer.[129] HT was administered 1-2 times weekly, for 5-6 treatments total. The median overall survival (mOS) for the CRT group was 12 months and the 1-year survival rate was 57% compared to 15 months and 80% for the CRT + HT group (p = 0.02). Taken together, these studies are encouraging for a benefit to the addition of HT to chemoradiotherapy in this population.

A retrospective study of patients with stage III/IV pancreatic adenocarcinoma who were treated with or without mEHT found improved response rates and overall survival in the mEHT treated individuals.[130] The majority of patients in both groups were treated with chemotherapy and/or radiotherapy (although fewer received treatment in the control group). After a median of 12.8 HT treatments, the rates of partial response were 64.7% and 8.3%, and stable disease rates were 29.4% and 27.8% in the mEHT and control groups, respectively. No statistical analysis was applied. The median overall survival in the mEHT group was 18 months (1.5-68 months) compared to 10.9 months (0.4-55.4 months) in the control group (p < 0.0017). The HT treatment was safe and well tolerated; a total of 22/499 (4%) AEs were attributed to HT. All were grade 1-2, and included skin pain (2%), grade 1 burns (1%), and grade 2 burns (0.4%).

One uncontrolled retrospective study evaluated HT use in patients with advanced pancreatic cancer with malignant ascites receiving intraperitoneal (IP) cisplatin and systemic gemcitabine chemotherapy.[131] HT was given twice weekly during a 4-week treatment cycle to 29 patients. Treatment was well tolerated, the response rate and disease control rate were 44.8% and 70%, respectively, and the mean overall survival was 195 ± 98 days (6.4 months). The authors reported that for this subgroup of patients, typical median survival is quite low at 63- 81 days.[136,137]

Lastly, a retrospective study evaluated a multimodal intervention including what the authors

termed "*metabolically supported chemotherapy*" (gemcitabine-based or FOLFIRINOX with insulin-induced hypoglycemia prior to treatment), ketogenic diet, hyperbaric oxygen therapy (HBOT), and mEHT.[132] Patients with metastatic pancreatic cancer were treated with HT and HBOT sequentially for 60 minutes each following the metabolically-supported chemotherapy. The median overall survival and progression free survival were 15.8 months (95% CI 10.5-21.2) and 12.9 months (95% CI 11.2-14.6) respectively. There were no toxicities attributed to the ketogenic diet, HT, or HBOT. The authors state that compared to studies using only FOLFIRINOX or gemcitabine-based chemotherapy in patients with metastatic pancreatic cancer, the survival outcomes were superior, and more research is warranted.

Prostate Cancer

Evidence at A Glance:

Three single arm trials,[138-140], two retrospective observational trials,[141,142] and one ongoing phase II trial,[143] have used HT in combination with radiation (RT) in men with non-metastatic prostate cancer. Due to limited and conflicting results, there is insufficient evidence to comment on the effectiveness of HT for men with prostate cancer.

Two of the retrospective trials compared HT administered 1-2x/week following intensity-modulated radiotherapy (IMRT) (n = 70[141] and n = 82[142]) to IMRT alone (n = 53 and n = 64). Neoadjuvant androgen deprivation therapy (ADT) was initiated prior to beginning the studies, but where the majority of patients (62%) continued ADT in Nakahara et al [141] , only 14% continued ADT in Yahara et al.[142] In Nakahara's study, the biochemical disease-free survival (bDFS) 5-year rates demonstrated a significant correlation between higher thermal doses of HT (> 7 minutes) and better bDFS (96.4% in 39 patients) compared to those who received HT for ≤ 7 minutes (81.5% in 31 patients, p = 0.0316), or who did not receive HT (82.9% in 51 patients, p = 0.0370). In contrast, Yakara et al found no significant difference in bDFS in the HT+RT group (82%) or 3-year bDFS (78%) group compared to radiation alone (81% and 72%, respectively; p = 0.30).

The largest single-arm trials evaluated patients with high-risk prostate cancer (n = 144), HT was delivered 1x/week within 15-30 minutes of RT for the duration of the treatment period, with some participants also on ADT.[138] 5-year overall survival was 87% and biochemical recurrence was 49%, with no significant acute or late toxicities reported. The smallest trial (n = 13) included patients with hormone-refractory locally advanced prostate cancer, administering HT (2x/week) 1 hour after RT, and reported that six participants achieved a complete response.[139] A trial including 21 participants with locally advanced prostate cancer administered HT for 60 minutes within one hour of radiation, and reported that at 36 months, 88% had survived and that the disease-free survival at 6 months was 25%.[140] The most recent trial (recruitment ongoing)[143] is a prospective multicenter non-randomized phase II study evaluating the safety, feasibility, and oncological outcomes of regional HT alongside salvage RT for patients with biochemical recurrence after radical prostatectomy. The interim analysis (n = 50) met safety criteria (one acute grade 3 hyperthermia-specific toxicity found) and feasibility, with no significant changes in QOL, although recruitment is ongoing.

Sarcomas and Soft-Tissue Tumors

Evidence at A Glance:

One RCT (yielding 3 publications),[144-146] six observational studies[147-152], and eight single-arm trials[153-160] included participants with soft tissue sarcoma. Additionally, one single arm trial[161] included a mix of advanced, deep seated sarcomas, and one observational study included patients with mixed soft tissue tumors.[162] Evidence demonstrates a benefit to progression-free survival and overall survival in patients with localized, high-risk soft tissue sarcoma (STS) treated with neoadjuvant and adjuvant HT with chemotherapy compared to chemotherapy alone. The evidence for the use of HT in other settings with sarcomas or other soft-tissue tumors is less clear.

A large, multi-centre RCT of regional HT for patients with localized, high-risk soft tissue sarcoma (STS) found the addition of HT enhanced the effect of chemotherapy resulting in improved patient outcomes.[144] The study, (EHSO-EORTC-62961 trial), randomized 341 adults with localized, high-risk STS (≥ 5cm, grade 2 or 3, deep to the fascia) to induction and post-induction chemotherapy alone, or chemotherapy plus RHT. Patients received four, 3-week cycles of doxorubicin, ifosfamide, etoposide chemotherapy with or without RHT administered on days 1 and 4. Following surgery and/or radiation, patients received another 4 cycles of their allocated treatment. Patients were then followed for up to 5 years. The first publication on these results was in 2010, after a median follow up of 34 months. The RHT arm had superior progression free survival (PFS) (HR 0.58, 95% CI 0.41-0.83, p = 0.003), and an absolute difference in PFS of 15% at 2 years (CI 6-26%) (76% RHT arm vs 61% control arm). Disease free survival (HR 0.70, 95% CI 0.54-0.92), treatment response rate (28.8% vs 12.7%, p = 0.002), and overall survival (HR 0.66, 95% CI 0.45-0.98) were also improved in the RHT arm compared to the control arm. Treatment was generally well tolerated, however grade III/IV leukopenia was greater in the RHT arm (77.6%, vs 63%, p = 0.005). RHT-related adverse events included pain, bolus pressure, and skin burn which was mostly mild to moderate, with ≤ 5% rated as severe. In 2018 a long-term analysis of the same study was published, to better assess survival outcomes.[145] This analysis found that after a median follow up of 11.3 years participants who received chemotherapy and HT, compared to chemotherapy alone, experienced a significantly improved local progression-free survival (HR 0.65; 95% CI 0.49-0.86, p = 0.002). Those receiving the combination treatment also experienced significantly prolonged survival rates compared to control (HR: 0.73; 95% CI: 0.54-0.98, p = 0.04). The EHSO-EORTC-62961 trial produced one additional publication in 2014 of a sub-group analysis of patients with abdominal or retroperitoneal high-risk STS.[146] The authors looked at PFS, DFS, and OS in 149 patients who had macroscopic complete resection of abdominal or retroperitoneal high-risk STS. The RHT plus chemotherapy arm had improved 5-year PFS (56% vs 45%, p = 0.044) and DFS (34% vs 27%, p = 0.040), but no difference in OS (57% vs 55%, p = 0.82).

Three of the observational studies included a comparator group, with one comparing to a Bone and Soft Tissue Tumor (BSTT) registry[147], and the other two to RT or CRT alone.[150,151] Compared to the BSTT registry, patients who received 60 minutes of HT simultaneously during CT (post-radiotherapy) experienced no significant benefit for 5-year overall

survival (78.3% vs 81.2%, p = 0.33). Local-control rate at 5-years was found to be significantly better in the hyperthermia group (97.7%) compared to control (85.1%) (p = 0.017). Regarding surgical outcomes, negative margins from definitive surgeries were significantly higher in the HT group (p < 0.0001). Two studies[150,151] which included a control group of CRT without HT both reported no statistically significant benefit for HT, including local control (p=0.39),[150] disease-free survival (p= 0.69)[150] and tumor response (p = 0.67).[151] One study[150] reported that cancer-specific mortality was significantly better compared to control (p = 0.03), while the other[151] showed no significant benefit (all > 0.05) for two-year overall survival, local-control survival or distant metastasis-free survival.

Three uncontrolled observational studies evaluated HT for STS. One included 64 participants with recurrent or residual STS who received HT with CRT (cisplatin, pirarubicin, and etoposide).[148] In this study, five-year survival was 86.4% (± 7.3%) and the local control rate was 86.7% (± 7.1%). Six participants experienced delayed wound healing due to skin burns. The second study included 110 participants with locally advanced high-risk soft tissue sarcoma (56 with metastases).[149] Participants received ICE chemotherapy (ifosfamide, carboplatin, etoposide) in addition to HT (with ifosfamide simultaneously infused during heating period). Disease control was achieved in 59% of non-metastatic cases and 47% in those with metastases, with a median overall survival of 26 and 12 months, respectively. Progression-free survival was significantly longer in the non-metastatic group (95% CI: 8-11 months) compared to those with metastases (95% CI: 2-5 months) (p < 0.0001). The third assessed participants (N = 27) with intermediate and high-grade retroperitoneal sarcomas treated with RT and neoadjuvant chemotherapy (doxorubicin and ifosfamide), 15 (56%) of whom additionally received deep regional HT.[152] Toxicity symptoms were not increased by the addition of HT. In younger patients and in those who received > 6 HT sessions, abdominal recurrence-free survival rates were slightly better in grade 2 compared to grade 3 tumors, though not statistically significant. the difference was not statistically significant (ARFS 80.8% vs. 78.6%, p = 0.74).

Eight single-arm trials evaluated HT in combination with a variety of treatments, including radiation and chemotherapy, with varying schedules based on surgery.

Two studies applied HT with chemotherapy, with the first[153] delivering HT in patients with high-grade soft-tissue sarcoma on days 1 & 4 of neoadjuvant chemotherapy (doxorubicin and etoposide) for 60 minutes. After 4 cycles, mean tumor volume reduction was 49% (5-91%, SD: 27%), with no signification correlation between necrosis before therapy (p = 0.1) or pre-treatment volume (p = 0.06) and tumor volume reduction observed. The second trial[154] included patients with doxorubicin/ifosfamide-refractory STS receiving chemotherapy (ifosfamide) and in 7 patients HT for 60 minutes on days 1 and 3. Two of the seven patients experienced a partial response.

Four single-arm trials explored the addition of HT to standard peri-operative care for patients with soft-tissue-sarcoma.[155-158] The oldest study of the five enrolled 13 patients to receive HT 2x/week for a total of 8-10 sessions (60 minutes at a time) in addition to radiation, with 5 participants receiving pre-operative chemotherapy and 7 post-operative chemotherapy.[157] Surgery (limb

salvage) was possible for 12/13 patients, with no events of local recurrence . Excluding one participant who died of heart disease, the 5-year survival was 40.4% and disease free-survival was 30.1%. Mean reduction in tumor volume was 68.2%, with no participants experiencing complete response, 7 experiencing partial response, 3 no change, and 3 progressing. The largest of the four studies enrolled 59 patients with advanced or recurrent high-risk STS and administered neoadjuvant chemotherapy (etoposide, ifosfamide and doxorubicin) with regional HT.[155] Patients later received surgical resection and adjuvant treatment. The overall objective response rate was 17%, with one complete (2%), and eight partial (15%) responses. At time of surgery, complete necrosis had occurred in 6 patients and > 75% necrosis in 12 patients. At treatment completion, 36 patients had no evidence of disease. The median overall survival (OS) was 52 months, and the 5-year survival rate was 49% (95% CI: 36-61%). Treatment-related toxicity was considered acceptable. A very similar study enrolled 58 patients and administered the same combination of HT with chemotherapy, in both the neoadjuvant and post treatment phase for patients with high risk soft-tissue sarcoma.[158] The overall objective response rate (based on 40 evaluable patients) was 13%, all of which were partial responses. Radiological response was 33%, and of the 30 who underwent treatment, 6 experienced pathological complete response (23%). Median time to local relapse or progression was 21 months, with median 5-year overall survival of 31 months. The final single arm trial, which combined data from two phase II trials, explored a combination of neoadjuvant chemoradiation and HT, followed by surgery and subsequent chemoradiation (without HT).[156] Objective response (evaluable in 39 participants) was 21% (1 complete and 7 partial), with a median overall survival of 105 months. The overall survival was 57%, with a 5-year local failure free survival of 48%.

Outside of peri-operative care, one study delivered HT in combination with neoadjuvant chemotherapy for patients with poorly resected, non-metastatic, soft tissue sarcoma.[159] Overall objective response was 16%, of which all were partial. Based on pathological assessment, 3 participants achieved complete response. Median time to local relapse or progression was 21 months, median OS was 33 months, and 4-year overall survival rate was 40%. The most recent proof-of-concept feasibility study[160] assessed the safety and tolerance of HT in addition to hypofractionated RT in patients with STS (n = 30) who were chemoresistant, had progressed after neoadjuvant chemotherapy, or who were not candidates for chemotherapy. Feasibility criteria of 90% was fulfilled (CI: 76-100, feasibility > 50%, $p < 0.001$), suggesting RT with regional HT is well-tolerated with no decrease in local efficacy of treatment.

Two studies included patients with malignancies other than STS. One single-arm trial included a mix of different deep seated, advanced sarcomas (43 soft-tissue, 12 Ewing's sarcoma, 7 chondrosarcoma and 3 osteosarcoma).[161] In addition to standard supportive care, patients received HT simultaneously with chemotherapy (ifosfamide, etoposide and mesna). Based on 61 evaluable patients, overall objective response was 34% (9 complete, 4 partial and 8 favourable). Additionally, 13 patients who were initially deemed to have unresectable disease, were able to undergo surgical resection. One observational study included patients with unresectable and/or recurrent mixed soft tissue tumors, applying a combination of HT and radiation.[162] This produced a

complete response in 42% of tumors treated, with a 5-year survival of 32%.

Vulvar & Vaginal Cancer

Evidence at a Glance:

There is insufficient evidence to comment on the efficacy of HT for patients with vulvar or vaginal cancer, as only one non-randomized clinical trial was identified.

A non-randomized controlled trial (n = 69)[163] of patients with vaginal or vulvar cancer receiving neoadjuvant chemotherapy (bleomycin or peplomycin + mitomycin C) alone or in conjunction with HT, reported a higher response rate in the HT group (63% vs 19%, no p-value provided) and significantly better long-term survival compared to control (data not presented). Given the lack of good quality data, no comment can be made regarding efficacy of HT for vulvar or vaginal cancer.

Studies Including Mixed Cancer Types

The studies below included patients with different types of cancer. When possible, studies have been grouped together when enrolled participants share similar pertinent characteristics. Due to the significant heterogeneity, no "evidence at a glance" statements are provided.

Abdominal and Pelvic Tumors

One RCT[164], one non-randomized controlled trial[165], and five single-arm trials[166-170] evaluated HT for mixed abdominal and pelvic cancers; all studies used a combination of HT with radiation and evaluated various outcomes. As all but two were single-arm trials, and cancer types and staging varied, it is difficult to draw conclusions about the overall efficacy of HT with radiation in this heterogenous patient population.

A multicenter, RCT (n=358)[164] investigated the use of radiation alone compared to combined radiation and HT for patients with either bladder, cervical or rectal cancer. Pooled results of all cancer types indicated that the intervention group experienced a significantly higher complete response rate compared to control (58% vs 37%, respectively, p = 0.003). Patients with cervical cancer experienced significantly better complete response (p = 0.003) compared to control, as did patients with bladder cancer (p = 0.01). No significant difference was noted for patients with rectal cancer. At the 3-year mark, patients with cervical cancer had significantly better overall survival compared to control (51% vs 27%, p = 0.009).

A phase I/II study enrolled 54 patients with locally advanced pelvic or abdominal tumors and administered HT 1-2x per week during radiation therapy.[166] Only 32% of patients completed the prescribed course of treatment, with patient discomfort as the main reason for discontinuation. Acute toxicities included three grade 4 (1 cutaneous, 1 infectious, 1 chemical peritonitis), one grade 3 (cutaneous), and 12 grade 2 (cutaneous, GI) adverse events. Late toxicities included one grade 4 (cutaneous), one grade 3 (GI), and six grade 2 (cutaneous, peripheral neuropathy) adverse events. Rates of CR and PR were 39% and 14% respectively. Local pain and discomfort were limiting features, with the HT technology at the time (1980s) likely being a primary contributing factor.

Thirty-seven patients with locally advanced deep seated tumors primarily in the pelvis (n = 34) were treated

with combined radiation and HT in a single-arm trial.[167] Acute toxicity was a limitation of treatment; in 60% of treatments the temperature or duration were limited, most often by pain within or around the applicator site, or discomfort due to treatment position. There were 9 treatment complications including skin burns, local infection/fever, epileptic seizure, perineal hematoma, and subcutaneous fat/muscle necrosis. Despite this, 64% of treatments achieved the temperature target of 42°C, and the objective response rate was 31%. The technology available at the time of this study (published in 1993), was likely a factor in the higher rates of complications observed.

One single-arm trial (n = 28)[168] focused on a mix of advanced upper-abdominal cancers, applying HT with radiation in 79% of the cohort. The overall objective response was 18% (all partial responses), and median overall survival was 4 months. Regarding symptom management, 43% were reported as having achieved "effective" palliation. Pain was commonly reported, resulting in HT delivery adjustments for 21% of cases. A similar pilot study[169], by the same group, was conducted in patients with deep-seated advanced pelvic or abdominal tumors (n = 46). HT (typically given 2x/week for 30 minutes), either right before or after radiation, resulted in an objective response rate of 67% for pelvic tumor cases and 9% for abdominal ones. Palliation was achieved in 83% of patients with pelvic tumors, compared to 54% in abdominal tumor cases. Median survival was 15 months (pelvic tumors) and 4 months (abdominal tumors). Patients with abdominal cancer experienced less adverse reactions and toxicity related to HT compared to those with pelvic cancer.

A non-randomized controlled trial[165] included patients with pelvic cancer refractory to treatment after definitive treatment, delivering either HT alone or in combination with radiation. In the combination treatment group, complete response was 18%, partial response was 50% and no change occurred in 32%. The HT alone group fared worse, with a complete response of 18%, partial response of 9% and 73% with no change. Pain relief, lasting > 2 months, was observed in 6 of 11 cases experiencing symptomology.

A single-arm trial[170] included 43 patients with deep seated pelvic tumors, receiving primarily HT + radiotherapy, of which 39 were evaluable for response. Overall objective response (CR + PR) was 49%, of which 5 were complete responses. A retrospective observational study[171] examined the incidence of acute neurotoxicity in 736 patients receiving hyperthermia for pelvic tumors. Acute neurotoxicity occurred in 17 of the 736 patients, with no association found between temperature or applied power and risk.

Genitourinary Cancers

Two single-arm trials[172,173] evaluated HT for mixed genitourinary cancers. One single-arm trial[172] included a mix of urological cancers (renal, urethral, bladder, prostate and retroperitoneal), receiving HT alone or in combination with radiation, chemotherapy or chemoradiation. Overall, 40/110 participants experienced objective response. Five-year survival was 48% for patients with bladder cancer, 29% for renal pelvic cancer, 25% for retroperitoneal and 0% for renal and prostate. There were 29/42 of participants assessed that reported pain relief with HT. A single-arm, phase I trial[173] included 53 patients with a variety of genitourinary cancers, who received HT 1-2x/week concomitantly with radiation (n = 44), chemotherapy (n = 6) or no additional treatment (n = 3). The 1-, 2- and 3-

year survival rates were 60%, 56% and 56% respectively, with complete response observed in 7 patients and partial response in 8.

Peritoneal Carcinomatosis

One RCT[174] and one phase I/II study[174] found encouraging preliminary results for the treatment of peritoneal carcinomatosis with the addition of HT. The RCT[174] enrolled 260 patients with peritoneal carcinomatosis with stage III-IV cancers (gastric, colon, rectal, pancreatic, endometrial, ovarian, and hepatic), and found that the addition of HT + TCM herbal treatment to standard intraperitoneal chemotherapy significantly improved objective response rate (77.69%) compared to control (63.85%) ($p < 0.05$). A non-significant difference was noted for complete response ($p = 0.063$) between groups. Karnofsky Performance Status significantly improved in the hyperthermia group (49.2%) compared to control (32.3%) ($p < 0.05$). The adverse event rate was significantly lower in the HT group (3 cases: 2.3%) compared to control (16 cases: 12.3%), with mild abdominal discomfort due to distention being the cause of treatment group AEs.

A phase I/II study found that the combination of regional abdominal HT and standard chemotherapy for patients with peritoneal carcinomatosis was well tolerated and encouraging for response.[175] Enrolled patients (n = 45) had peritoneal carcinomatosis from colorectal cancer, ovarian cancer, gastric, pancreatic, and/or biliary cancer. The 3-year OS for colorectal cancer was 22% and for ovarian cancer was 29% which the authors deemed as encouraging. For pancreatic, biliary, and gastric cancers the results were not as promising, with a 1-year OS rate of 25% and mOS of 7 months. The response rate, as defined by symptom palliation and reduction in tumor markers was 68.7%. There was no evidence of heat-specific toxicities, and chemotherapy toxicities were no different from expected.

Liver Metastases

Three small studies, two observational[176,177] and one single-arm trial[178] reported on HT administration for liver metastases. A case-controlled observational study including 64 participants with either primary liver cancer or hepatic metastases from other malignancies, reported on the use of HT combined with intra-hepatoarterial chemotherapy.[176] Compared to chemotherapy alone, the partial response rate was higher in the HT combination group (28% vs 37%, respectively), however statistical analysis for significance was not provided. A small observational study[177] (n = 16) reported that the combination of HT and intra-arterial radioactive microspheres resulted in 4 patients with liver metastases achieving disease control. A single-arm trial[178] included 49 patients with hepatic metastases, for whom HT was administered either alone or in combination with radiation, chemotherapy or radiochemotherapy. Complete response occurred in 2 patients, partial response in 4, no response in 10, and the rest progressed. The median duration of response lasted 26 weeks. Median survival was 25 weeks, with no significant differences observed between groups ($p = 0.07$).

Cervical Lymph Node Metastases

Local HT was combined with radiotherapy in a phase II trial for the treatment of metastatic squamous cell carcinoma to cervical lymph nodes from an unknown primary in 15 patients.[179] This study administered HT 2x/week (total of 2-7 sessions/participant) during definitive radiotherapy. The objective response rate was 86.5% (9 CR, 4 PR), local control and survival at 5 years

was 54.5% and 29% respectively. Acute and late toxicities were mild and included pain during HT, moist skin desquamation, and one case of cutaneous necrosis.

Brain Metastases

Fifteen patients with brain metastasis and poor prognosis (Graded Prognostic Assessment (GPA) score ≤ 2.5) were enrolled in a prospective observational study.[180] Participants received HT 2x/week in addition to radiotherapy and systemic treatment. PFS was longer in patients with longer HT effective treatment time (> 88% W90time [the percentage of total treatment time at 90% of prescribed energy]) compared to those with shorter effective treatment time (100% vs. 50% at six months and 66.7% vs. 0% at 12 months, p = 0.030). Patients with GPA score 0-1 had a median OS of 3.0 ± 0.26 months (95% CI 2.49–3.51) compared to a median OS of 8.0 ± 1.45 months (95% CI 5.15–10.84) in patients with 1.5-2.5 GPA score. All patients received all planned HT sessions and completed the planned RT and/or systemic treatment with no acute toxicity reported. The authors reported that in brain metastases patients' regional HT is a feasible and safe technique to be used with RT.

Superficial Tumors

Four studies evaluated HT combined with radiation for superficial tumors,[181-184] one retrospective study evaluated HT with chemoradiotherapy,[185] and one single-arm trial used HT and chemotherapy.[186] Generally, combined HT with RT achieved good results and was superior to RT alone.

A non-randomized controlled phase I/II study evaluated HT alone, HT with radiation (RT), or RT alone in patients with superficial metastases (n=116 lesions).[181] The complete response rate for patients receiving RT + HT at an adequate temperature (43°C for at least 23 minutes) was superior to patients receiving RT alone or RT + HT but heated to an inadequate temperature (86% versus 35%, p < 0.05). Treatment with HT-alone had a poor complete response rate (11%). Two studies used HT with RT or RT alone on different superficial lesions within the same patient and found superior response rates to combined treatment. The first study evaluated this treatment in 85 lesions (53% were of mammary origin) in 38 patients.[182] The response rate (CR + PR) for combined treatment overall was 76%. In a subset of 18 patients with 2 or more lesions who received combined treatment for one or more and RT alone for one or more lesions, the combined treatment was superior to RT; response rates were 89% vs 50% respectively (p = 0.0039). In the other single-arm trial[183] similarly implemented lesion "controls" were applied in participants who had two superficial malignancies. Combination treatment (RT + HT) resulted in quicker lesion regression and an initial overall response of 97% compared to 58% for controls. At 6 months, none of the heated lesions failed to response, with 27/31 achieving complete response compared to 12/31 for controls (p < 0.01). Recurrence rate per 6-month interval was significantly better for lesions treated with the combination intervention (p < 0.05). A small single-arm trial[184] used two different HT machines in patients with superficial tumors in addition to radiation. Those using the Aloka system experienced a complete response rate of 55% (16/30 patients), and those using the BSD-1000 system achieved complete response in 30% of cases (10/33 patients).

A small (n = 13) single-arm pilot study[186] combined HT with chemotherapy in patients with superficial metastases from various histological

malignancies. HT delivered simultaneously during chemotherapy infusion resulted in an overall response rate of 54%.

A retrospective observational study[185] from 1993, including 18 patients, explored the use of HT for head, neck and upper chest wall superficial tumors that were inoperable and refractory to conventional treatment. Participants received HT right after radiation treatment, while receiving intravenous chemotherapy. Overall, the response rate was 61.1%, with 3/18 experiencing complete response and 8/18 partial response. No clear associations were noted between total HT sessions or histological type and tumor response, whereas there seemed to be a correlation between better efficacy with higher intra-tumoral temperatures.

Mixed Advanced Cancers

One study found that combined treatment with radiofrequency regional HT (RFRH) and standard or high dose mitomycin C was superior than either treatment alone for the treatment of mixed advanced cancers.[187] The study evaluated 99 adults (53 had primary or metastatic liver cancer) treated with radiofrequency RHT (group 1), standard dose mitomycin C (group 2), combined treatment (group 3), and combined treatment with high dose mitomycin C or Adriamycin with charcoal hemoperfusion (group 4). A greater than 50% tumor reduction was observed in 9%, 0%, 25%, and 55% respectively, and the median OS of those with primary or metastatic liver cancer was 2.7 months, 4.5 months, and 9.5 months for groups 1, 2, and 3+ 4 respectively. While the results favor the combined treatment, no statistical comparison was performed.

A single-arm trial of HT combined with standard of care radiation therapy with or without systemic chemotherapy found RHT to be safe and feasible in patients with mixed locally advanced or metastatic cancers.[188] Patients received RHT 2x/week during RT. They reported that 86.8% of lesions received the planned HT treatments, and only 13/159 lesions (n=12 patients) discontinued treatment due to heat intolerance. Grade 0-1 toxicity was reported in 138/151 lesions, and only 13 sites (8.6%) reported a grade $\geq$ 3 toxicity.

A large phase I trial (n = 353)[189] included a mix of advanced or recurrent cancers, with the majority being GI adenocarcinoma (n = 146), genitourinary cancer (n=86), soft tissue sarcoma (n = 46) and melanoma (n = 21). HT was typically delivered 2x/week for 8 sessions, followed by 1-2x/week for 4-5 additional sessions. Participants either received HT alone (n = 47), in combination with radiation (n = 260), in combination with chemotherapy (n = 42) or in combination with both radiation and chemotherapy (n = 15). Complete response occurred in 35 patients (10%) and partial response in 59 (17%). Overall, 2-year survival was 15%, with a median time of 42 weeks. Pain improved completely in 44/195 who reported it at baseline, with 77 additional participations reporting partial resolution. Sub-group analysis revealed that the complete response rate was 12% for those who received radiation compared to 2% for those who did not (p = 0.003).

A single-arm trial[190] combined HT with conventional care (chemotherapy and/or radiation, with or without surgery) in a mix of advanced cancers (n = 107) including liver, colon, breast, sarcoma, lung and head & neck. Response rates were only reported for the most common histological types of tumors treated. 12/17 patients with colorectal cancer experienced partial response, 7/14 of patients with HNC experienced

complete response and 4/14 experienced partial response, 3/8 patients with breast cancer experienced complete response and 4/8 partial response, and finally 5/7 patients with sarcoma experienced partial response. Overall HT was generally well tolerated. For all patients, the complete response rate was 16%, with a partial response rate of 52%. Pain relief was also often reported by participants.

Miscellaneous Mixed Cancers

A single-arm trial including patients with breast cancer (n = 10), HNC (n = 9) and sarcoma (n = 9)[191] delivered HT in addition to radiation and chemotherapy. Regardless of treatment regimen and cancer type, hyperthermia was delivered in close proximity with CRT. With a mean follow up time of 13.5 months (3-46 months), the overall response rate in patients with breast cancer was 100% (70% achieved complete response), and the overall response rate for those with either HNC or sarcoma was 75% (19% experienced complete response). Toxicity and adverse events were mild, other than one patient who was reported to be obese and sustained subcutaneous necrosis due to excessive tissue heating.

Other Studies Not Described in Detail

There are several small pilot and other uncontrolled studies published prior to 2000 assessing HT alongside various other treatments in mixed cancer-types primarily for feasibility. These studies generally found reasonable safety and variable response rates**.** However, due to small and heterogeneous populations, lack of comparator, older technologies used, and use of cancer treatments not commonly used anymore, these studies will not be discussed individually in detail but are included here for reference.[192-204] Some studies published in the 1980s found acute toxicity to be a concern, particularly for RHT of deep seated tumors.[167,194,197]

Quality of Life Support & Symptom Management

A few studies have explored to the use of HT for improving quality of life (QOL) and managing symptoms, such as pain. The data is considerably limited, and thus conclusions cannot be drawn. As a result, QOL support is not recommended as the main indication for HT use.

QOL and symptom management have been reported in a few studies of women with gynecological cancers using HT. In a single-arm trial, patients with ovarian cancer received weekly IV Doxil and HT for 6 cycles or until disease progression. Overall, QOL was found to be above average at baseline and did not significantly change between timepoints, possibly signaling maintenance.[118] In another study, including patients with cervical cancer receiving HT and chemoradiotherapy, multiple QOL endpoints were tested.[35] At the 6 week point, mean change in cognitive functioning was significantly better than control ($p < 0.05$). At the 3-month timepoint, post-treatment fatigue and pain were also significantly better than the control group ($p < 0.05$). Both social functioning ($p = 0.049$) and emotional functioning ($p = 0.017$) significantly improved. A third single-arm trial in patients with cervical cancer receiving HT and conventional care reported that for patients experiencing pain, palliation was achieved in 74% of participants.[42]

Pain management using HT was also explored for patients with rectal and colorectal cancer. One single-arm trial assessed 17 participants and found that 70%

experienced decreases in subjective pain scores compared to baseline.[47] One uncontrolled observational study assessed pain score changes in patients with colorectal cancer receiving both chemotherapy and HT.[64] Complete pain resolution was noted in 22% of participants (n = 9), with 37% having "good" pain relief (n=15). The median duration of pain relief was seven months. Patients with unresectable and chemotherapy-refractory liver metastases due to colorectal cancer receiving radiation did not appear to benefit from the addition of HT for QOL. However, 4/10 participants experienced pain relief, but this did not last to the 3-month timepoint.[65]

Both QOL and symptom palliation was assessed in a small single-arm trial for patients with HNC receiving HT with or without radiation with recurrent cancer positive cervical lymph nodes post-surgery.[86] Overall symptom palliation (pain, bleeding, breathing, swallowing and speaking) was achieved in 19/20 patients.

Three studies, including one RCT[100], one case-control study[106], and one retrospective chart review[107] explored the use of HT for QOL and symptom management in patients with lung cancer. The RCT administered a combination of HT, IVC and basic supportive care in the treatment arm for patients with refractory NSCLC (stage IIIb-IV).[100] Authors reported that in the treatment arm, significant improvements in QOL were noted for physical, emotional, and global measures. Pain, fatigue, nausea, SOB, and appetite loss were also found to significantly improve. The case-control trial retrospectively evaluated changes in cancer-related pain for patients with NSCLC receiving standard treatment, with one group also receiving HT.[106] Using the Effective Analgesic Score (EAS) tool to assess changes in pain, it was found that pain increased in the treatment arm at the first time point but a non-significant decrease occurred by the third time point compared to the control arm. Authors hypothesize this was due to the initial effects of HT. A chart-review of patients with malignant mesothelioma receiving palliative radiotherapy reported that the addition of HT appeared to improve both pain control and duration.[107]

Hyperthermia as Monotherapy

Very few studies have evaluated HT as a monotherapy, and the results have not been encouraging.[123,165,181] Clinical effectiveness has only been demonstrated for the application of HT with chemotherapy and/or radiotherapy.[16,17] Thus, HT is not currently recommended as a monotherapy for cancer until more information is available.

Table 1: Systematic Reviews and Meta-Analyses of LRHT for Cancer

Reference	Study design	# of trials and participants	Population	Intervention	Control	Results
Hu et al, 2017[68]	Systematic review and meta-analysis	19 RCTs (n = 1519)	Esophageal cancer - mixed staging	Hyperthermia chemo-radiotherapy (HCRT)	Chemo-radiotherapy (CRT) or radiotherapy (RT)	HCRT vs CRT: 1-, 3-, 5-, 7-year survival: OR and 95% CI 1.79, (1.12, 2.84, P = 0 01), 1.91, (1.27, 2.87, P = 0.002), 9.99, (1.72, 57.91, P=0. 01), and 9.49, (1.14, 79.27, P = 0.04) respectively. 2-year survival was not significantly different. Complete response rate: OR 2.00, (1.49, 2.69, P < 0.00001) Safety: Decreased GI reactions, leukocytopenia, radiation-esophagitis (OR 0.43, 0.49, 0.43 respectively, P < 0.0001) HCRT vs RT: 1, 2, 3, 5 year survival: OR and 95% CI 3.20 (2.07, 4.95, P < 0.00001), 2.09 (1.13, 3.85, P = 0 02), 2.43 (1.67, 3.51, P < 0.00001), 3.47, (1.08, 11.17, P = 0.04) Complete response rate: OR 2.12, (1.29, 3.47, P = 0.003) Safety: No statistically significant differences, however HCRT trended toward higher rates of GI reactions, leukocytopenia and radiation oesophagitis and a trend of lower rates of radiation pneumonitis.
Datta et al, 2016[30]	Systematic review and meta-analysis	Conventional meta-analysis: 6 RCTs (n = 427) Network meta-analysis: 8 trials (7 RCTs, 1 meta-analysis, n = 1160)	Cervical cancer – locally advanced (stage IIb – Iva)	Hyperthermia radiotherapy (HTRT) and Hyperthermia chemotherapy radiotherapy (HCRT)	Radiotherapy (RT) and chemoradiotherapy (CRT)	Conventional meta-analysis of HTRT vs RT: Complete Response: HTRT vs RT, OR 2.67 (95% CI 1.57-4.54, p < 0.001), NNT 4.5 Locoregional control: HTRT vs RT, OR 2.61 (95% CI 1.55–4.39, p < 0.001), NNT 4.3 Survival: HTRT vs RT, OR 1.94 (95% CI 1.10-3.40, p = 0.021) Toxicities: no significant differences in acute or late toxicities Network meta-analysis: Complete response: HCRT was superior to CRT (OR 2.91, 95% CI 1.97-4.31), and RT (OR 4.52, 95% CI 1.93-11.78). Survival: HCRT was superior to CRT (OR 2.65, 95% CI 1.51-4.87) or RT (OR 5.57, 95% CI 1.22-23.42). Rankogram and SUCRA values showed the best option for response and survival was HCRT followed by HTRT

Lutgens et al, 2010[31]	Systematic review and meta-analysis	6 RCTs (n = 267)	Cervical cancer - locally advanced (stage 2b-4a) *Most had stage IIIb	Hyperthermia + radiotherapy (HTRT)	Radiotherapy (RT)	Combined HTRT had superior outcomes for: Complete response: RR 0.56, 95% CI 0.39 - 0.79, p < 0.001 Local recurrence rate: RR 0.48, 95% CI 0.37-0.63, p < 0.001 Overall survival: HR 0.67, 95% CI 0.45-0.99, p = 0.05 Toxicities: no significant difference in acute or late toxicity between arms.
Van der Horst et al, 2018[135]	Systematic review	14 studies (n = 395); 8 studies used LRHT (n = 189) None were RCTs, all were observational (8 retrospective, 6/14 included a Ctrl group)	Pancreatic cancer – locally advanced or metastatic	Hyperthermia (locoregional, whole body, intraoperative)	Radiotherapy and/or chemotherapy (Chemotherapy in 60%, chemo/rads in 33%, radiation alone in 7%)	Response rate (11 studies): 31.3% In 3/11 studies with a control group, response rate was 43.9% in HT group vs 35.3% in control group. Survival (12 studies): 10.5 months. For 6/12 studies with a control group, median OS was 11.7 months (6-18.6) in HT group, vs 5.6 for control group (4-11). Safety: The only severe hyperthermia-related AE was subcutaneous fatty burn in one patient receiving intraoperative hyperthermia. Authors noted that because quality of studies were limited and none were randomized, a full meta-analysis was not performed. These results were not exclusive for LRHT, but combined multiple types of HT.
Datta et al, 2016[81]	Systematic review and meta-analysis	6 studies: 5 RCTs, 1 non-randomized controlled trial (n = 451)	Head and neck squamous cell carcinoma – mostly stage III/IV	Hyperthermia + radiotherapy (HTRT) (locoregional in 5/6, intracavitary in 1/6)	Radiotherapy (RT)	Complete response: RT alone: 39.5%, HTRT: 62.5%, OR 2.92 (95% CI 1.58–5.42, p = 0.001) The corresponding risk reduction was 1.61 (95% CI 1.32–1.97, p = 0.0001, I^2 = 13.37, p = 0.329) and risk difference 0.25 (95%CI 0.12–0.39, p = 0.0001, I^2 = 59.44, p = 0.031) No increase in toxicities with HTRT compared to RT alone.
Datta et al, 2015[25]	Systematic Review and Meta-Analysis	31 papers (reporting on 34 studies); 6 single-arm studies, 5 RCT's, 3 non-randomized controlled (n = 1792)	Breast cancer - Local/regional recurrence	Hyperthermia + radiotherapy (HTRT) HT most often applied 2x/week following radiation, mean temperature 42.5 °C	Radiotherapy (RT)	<u>Controlled clinical trials:</u> Mean complete response rate: HTRT: 60.2% vs Radiotherapy: 38.1% (OR: 2.64; 95% CI 1.66-4.18, p < 0.0001) Single-arm studies: HT group complete response: 63.4% (Event Rate 0.64; 95% CI: 0.57-0.66)

Longo et al, 2016[18]	Systematic Review	16 studies; 8 single-arm trials, 1 RCT, 1 non-randomized trial, and 6 observational studies (4 retrospective, 2 prospective) (n=346)	Bladder cancer - mix of muscular-invasive and non-muscular invasive	Hyperthermia with chemotherapy and/or radiation and/or surgery Temperature ranged from 38°C-45.5°C	Mixed conventional care alone	Recurrence free survival at 24 months was reported in two single-arm trials, with one being 78% and the other 33%. Complete response rate (one non-randomized controlled clinical trial): 54.5% in HT group vs 35% in the control group (p-value not provided) OS (one RCT) not significantly different between groups (28% vs 22%, p > 0.05)

Table 2: Randomized Controlled Trials of LRHT For Cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Issels et al, 2010[144]	Multicentre phase III, open label RCT, (EORTC 62961-ESHO 95 Trial)	N = 341 (tx 169, ctrl 172) **Soft tissue sarcoma (STS)** – adults with localized STS (tumor 5cm or greater, FNCLCC grade 2 or 3, no distant metastasis)	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting 42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Primary outcome: local PFS Secondary outcomes: DFS, OS, tumor response, toxicity Follow up was 5+ years	Local PFS: HT group less likely to progress than control group, relative hazard 0.58, (95% CI 0.41-0.83, p = 0.003) Absolute difference at 2 years of 15% (95% CI 6-26, 76% HT vs 61% control) DFS: relative hazard 0.70 (95% CI 0.54-0.92, p = 0.011) for tx compared to control. Tx response rate: 28.8% tx group, 12.7% control group (p = 0.002). OS was better in tx group (HR 0.66, 95% CI 0.45 - 0.98), p = 0.038 Toxicity: HT-related AEs: mostly mild to moderate (less than 5% severe): pain, bolus pressure, skin burn. Increased leucopenia in tx arm vs ctrl arm (77.6% vs 63%, p = 0.005)
Angele et al, 2014[146]	Subgroup analysis of (EORTC 62961 -ESHO 95 Trial) Phase III, multicentre, open label RCT	N = 149 (subgroup of the total 341 population) **Soft tissue sarcoma (STS)** – adults with abdominal or	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Local PFS, DFS, OS after 5-year follow-up	Local PFS: 56% in tx arm vs 34% in ctrl arm (p = 0.044) DFS: 34% in tx arm vs 27% in ctrl arm (p = 0.04) OS: no difference between groups (57% vs 55% in tx vs ctrl)

		retroperitoneal high-risk sarcoma, who had macroscopic complete resection (R0, R1).	42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT			
Issels et al, 2018[3]	Long-term outcomes of the EORTC 62961 - ESHO 95 Trial Phase III, multicentre, open label RCT	N = 341 (tx 169, ctrl 172) **Soft tissue sarcoma (STS)** – adults with localized STS (tumor 5cm or greater, FNCLCC grade 2 or 3, no distant metastasis)	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting 42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Primary: local PFS. Secondary: OS At a median follow up of 11.3 years	PFS: improved in tx arm, HR 0.65 (95% CI 0.49-0.86, p = 0.002) OS: HR 0.73 (95% CI 0.54-0.98, p = 0.04) with 5-yr survival of 62.7% vs 51.3%, and 10-yr survival or 52.6% vs 42.7%. Absolute differences in survival at 5 and 10 years were 11.4% and 9.9% respectively. Both differences reported to be statistically significant ($p < 0.05$)
Fang et al, 2019[205]	RCT	N = 118 (tx 55, ctrl 63) **Gastric cancer** – stage III/IV	Regional HT + chemotherapy (HTCT). Chemotherapy was a 3-week cycle of IV oxaliplatin and oral S1. HT was administered twice weekly (60 minutes, target temperature 42-43°C) from start to end of chemotherapy.	Chemotherapy alone	Objective response rate (ORR) (CR + PR) Disease control rate (DCR) (CR, PR, SD) OS Safety	Disease control rate: 70.9% and 46.0% for HTCT and Ctrl groups respectively (p = 0.006) mOS 23.5 months for HTCT group and 14 months for Ctrl (p = 0.01) 3-year survival rate: RHCT 11.4%, Ctrl 0% (p = 0.018) Safety: No difference in grade 3/4 AEs ORR was not reported on in the study, however from looking at the table it appears there was no difference as no one experienced a complete response
Guo et al, 2007[111]	RCT	N = 18 (tx 9, ctrl 9) **Metastatic melanoma** - refractory to other treatments, with an accessible tumor mass	Local HT + intratumoral dendritic cell (DC) injections HT administered for 1 hour prior to DC injection (42-43 C), 3x in week one of a 28-day cycle, up to 2 cycles administered.	Intratumoral injection of dendritic cells (DC) alone	Objective response rate (CR + PR) and disease control rate (CR + PR + SD) Time to progression (TTP) Survival Toxicity Melanoma-specific antitumor immunity	DC Response: 77.8% in Tx arm, 44.4% in Ctrl arm, $p < 0.05$. Tx arm: 1 CR, 3 PR, and 3 SD. Ctrl arm: 1 PR and 3 SD. TTP: 5 months and 2 months Tx and Ctrl arm respectively ($p < 0.05$) Median survival: No significant difference (13 months vs 6 months, $p > 0.05$). Safety: 42 AEs in Tx arm, 19 AEs in ctrl arm.

						Grade 1/2 lymphopenia was the most common AE in treatment arm, other AEs included: sweating, vomiting, malaise, which all recovered within 24-48 hours. Antitumor immunity: Cell assays demonstrated some possible anti-tumor immune effects of LHT: induction of cytotoxic T lymphocytes, heat shock protein expression, enhanced Th1/Th2 chemokine production, promoted migration of DC to afferent LNs.
Overgaard et al, 1995[33]	RCT	N = 70 (134 malignant lesions) **Melanoma** - recurrent or metastatic melanoma lesions	Radiation + HT 3 fractions of radiation over 8 days, followed by 1-hour HT at target temperature of 43°C	Radiation alone	CR (at 3 months) Persistent local control Safety	CR: 62% in Tx arm, 35% in Ctrl arm ($p < 0.05$) 2-yr local tumor control: 28% in radiation alone vs 46% in combined treatment ($p = 0.008$) Most important prognostic variables: hyperthermia (OR 2-yr local control: 1.73, 95% CI 1.07-2.78, $p = 0.023$), radiation dose, tumor size. Safety: Addition of heat did not increase acute or late effects of radiation.
Minnaar et al, 2019[33]	Phase III RCT, preliminary results	N = 202 (tx 101, ctrl 101) **Cervical cancer** - FIGO stages IIB to IIIB SCC, treatment naïve. Patients recruited from a low-resource setting, and could be HIV+ or negative.	Modulated electrohyperthermia (mEHT) + chemo-radiotherapy (cisplatin) mEHT administered 2x/week immediately before radiation, to the pelvis, at a temperature of 42.5°C for a minimum of 55 minutes.	Chemo-radiotherapy alone	Primary: local disease control (at 6-months) Secondary: Toxicity (CTCAE) QOL Survival	Local disease control: higher in mEHT group (n = 40, 45.5%) compared to control (n = 2, 24.1%), $p = 0.003$ Local DFS: mEHT group, n = 39 (38.6%), control n = 20 (19.8%), $p = 0.003$ Toxicity: mEHT did not affect frequency of CRT-related early toxicities. Tx was well tolerated; 11 mEHT participants reported AEs: grade 1-2 adipose tissue burns, grade 1 surface burns. QOL: at 3 months post-tx, fatigue and pain were reduced in the mEHT group and there was significant improvement in social function, emotional function. No differences between groups while on treatment.
Harima et al, 20016[32]	Multicentre, open label, RCT	N = 101 (tx 51, ctrl 50)	HT + chemoradiotherapy Whole-pelvis hyperthermia (43°C) delivered once weekly concurrently with	Chemoradiotherapy alone (cisplatin)	5-year survival, response rate, DFS, LRFS, AE/toxicity	Overall-5-year survival: No significant difference between HT group (77.8%) and control (64.8%). $P = 0.077$).

		Cervical cancer - stage IIA-IVA, treatment naïve	cisplatin + radiotherapy for 60 minutes, delivered for the duration of 3-5 chemoradiotherapy cycles			DFS: Not significantly different between both groups (p = 0.183), with adjusted HR also showing no significant difference (p = 0.73). LRFS: No significant difference between groups Complete response: No significant difference between groups. Adjusted complete response rate showed a significant difference (p = 0.047) AEs were similar between groups
Mitsumori et al, 2007[98]	Multicentre, open label, RCT	N=80 (tx 40, ctrl 40) **NSCLC:** Locally advanced, stage II-III	HT + radiation HT delivered for 60 minutes/session, once a week (minimum 5 sessions), in addition to radiation	Radiation alone	Survival, response, PFS, toxicity	1-year local PFS: Significantly higher in the HT group (67.5%) compared to control (29.0%) (p = 0.036). 1-year overall survival: Not significantly different between groups (p = 0.868).
Shen et al, 2011[97]	Phase II RCT	N = 80 (tx 40, ctrl 40) **NSCLC:** advanced, stage IIIB-IV	HT + chemotherapy One hour after chemotherapy (cisplatin + gemcitabine), patients received HT (300-1100 W), for 60 minutes, 2x/week. Target temperature 39-42.5 °C.	Gemcitabine + Cisplatin, without HT	Tumor response, toxicity/AE, QOL, Clinical Benefit Response (CBR)	Response rate: No significant difference between groups Global QOL: HT group significantly compared to control, however, no differences among specific components.
Shchepotin et al, 1994[76]	Three-armed RCT	N = 293 - Surgery alone = 100 - Radiotherapy + Surgery = 98 - Surgery + Radiotherapy + HT = 95 **Gastric cancer**: non-metastatic	HT + radiation HT was delivered 2 hours after radiation, for 60-70 minutes, everyday for 4 consecutive days prior to surgery (pre-operative phase). Tumor temperature target >42°C.	Surgery alone or surgery + radiation therapy alone	Survival	3- or 5-year survival: Hyperthermia + radiation did not significantly improve either compared to radiation alone. Compared to surgery alone, radiation + hyperthermia significantly improved 5-year survival p < 0.05.
Petrovics et al 2016[206]	RCT Pilot Study	N = 50 (tx 25, ctrl 25) Mix of cancer types – all patients suffering from chronic fatigue syndrome	HT + Biobran (MGN-3-arabinoxylane) HT delivered 1x/week for 15 weeks. Unclear if they also received standard care	Standard care (chemotherapy and radiation)	QOL, fatigue	Whole-body pH: Compared to baseline, the HT group is reported to have significantly improved their (p < 0.01) Antioxidant status: significantly improved compared to baseline in HT group (p < 0.01).

						Fatigue: significantly improved in the HT group ($p < 0.01$), with no change noted in control group.
Pang et al, 2017[174]	Phase II RCT	N = 260 (tx 130, ctrl 130) **Mixed peritoneal cancers:** stage III-IV with the presence of malignant ascites	HT + TCM herbal medicine HT was 60 minutes, every 2nd day for 4 weeks (14 total sessions)	Standard intraperitoneal chemotherapy	Response, QOL, Pain	Objective response (CR + PR): Significantly higher in the Tx group (77.69%) compared to control (63.85%) $p = 0.005$. A non-significant benefit was noted for complete response in the Tx group compared to control. KPS score: significantly improved in Tx group compared to control $p < 0.05$. Adverse Events: occurred significantly more in the control group (16 cases) compared to Tx group (3 cases) $p < 0.05$
Ou et al, 2017[207]	Phase I RCT	N =15 (5 in each arm) **NSCLC:** stage III-IV, all receiving standard treatment within the past 6 months	HT + IVC HT 3x/weeks for 4 weeks (60 minutes at 40-42°C), before, during, or after IVC.	All three arms received HT, however, timing of IVC varied (prior, during or after HT)	QOL, AE,	Pertaining to QOL, the only measure that significantly improved compared to baseline was physical functioning. No significant between-group QOL differences/changes were found.
Ou et al, 2020[100]	Phase II RCT	N = 97 (tx 49, ctrl 48) **NSCLC:** stage IIIb-IV, heavily pre-treated and refractory to prior Tx	HT + IVC + basic supportive care HT 3x/week (60 minutes, 40-42°C), simultaneous to IVC (1g/kg), 3x/week.	Basic supportive care alone	Response, PFS, disease control rate, survival, AE, QOL	Median OS: 9.4 months in Tx group compared to 5.6 months in control (HR 0.33, 95% CI 0.16-0.41, $p < 0.0001$. Median PFS: 3 months in the Tx group compared to 1.85 months in control (HR 0.33; 95% CI 0.12-0.32, $p < 0.0001$). 3 Month Disease Control Rate: 42.9% in Tx group compared to 16.7% in control ($p = 0.0073$). QOL: physical, emotional, and global improvements were significantly better in the Tx group. Significant improvements were noted for symptoms such as fatigue, pain, nausea, SOB and appetite loss in the Tx group compared to control. Biomarker Changes: no significant changes observed
Minnaar et al, 2020[35]	Phase III RCT	N = 206 (tx 101, ctrl 105)	HT + radiation + cisplatin	Radiation + cisplatin alone	Toxicity, QOL	QOL: At the 6-week mark, cognitive function was significantly higher in the HT group compared to control.

		Cervical cancer: stage IIB-III, HIV positive (CD4+ count > 200)	Immediately before radiation, patient received HT for 55 minutes, 2x/week. Patients also received cisplatin.			At the 3-month mark, fatigue and pain were significantly reduced in the HT group. At the 3-month mark, compared to baseline, social functioning significantly improved.
Minnaar, et al, 2020[14]	Phase III RCT *Sub-analysis of Minnaar et al, 2020[35]	N = 108 (54 in each) **Cervical Cancer:** Tx group: 25 HIV+, 29 HIV- Ctrl group: 26 HIV+, HIV- Participants included in this sub-analysis if they had nodes outside the treatment field and were evaluated 6-months post treatment	HT + radiation + cisplatin Immediately before radiation, patient received HT for 55 minutes, 2x/week. Patients also received cisplatin.	Radiation + cisplatin alone	Evidence of an Abscopal effect (based on complete metabolic resolution)	Evidence of complete metabolic response (CMR) was significantly higher in the HT group (24.1%) compared to control (5.6%) (p = 0.013).

Van der Zee et al, 2000[164]	Multicentre RCT	N = 358 (tx 182, ctrl 176) **Mixed Cancer:** bladder cancer (T2-T4, N0, MO), cervical cancer (stage IIB-IV) or rectal cancer (M0-1)	HT + RT HT 1x/week, 1-4 hours post radiotherapy (total of 5 Tx). Target temperature 42°C.	Radiation alone	Response, local control, survival	Complete Response: Pooled analysis indicated that this was significantly higher in the HT group compared to control (58 vs 37%, respectively, p = 0.003). Patients with cervical cancer and bladder cancer, had rates of complete response that were significantly better than control (26% and 22%, respectively, p = 0.003 and p = 0.01, respectively). No significant difference was noted for rectal cancer. Patients with less advanced disease had better response than those with higher tumor stages (p = 0.007). Adjusted duration of local control: Improved more in the intervention arm (p = 0.01). Survival: Mean odds of mortality between groups was not significantly different (p = 0.16). At 3-year follow up, only patients with cervical cancer had a significantly better overall survival (51% vs 27%, p = 0.009).

Wang et al 2020[36]	RCT	N=345 (tx191, ctrl 82) **Cervical cancer:** FIGO stage IB-IV	HT + CRT HT: 2x/week for total of 6 treatments, initiated during the 3rd week of RT, within 1 hour prior to RT and after chemotherapy. Target temperature of 40.5 C for 60 minutes.	CRT alone	Survival, loco-regional relapse free survival, acute and Late toxicity	<u>5-year OS</u>: HT +CRT group demonstrated better OS (81.9 % vs 72.3%, p = 0 .040). <u>5-year local relapse-free: survival:</u> No significant difference between groups (86.8% vs 82.7% in HT vs control, p = 0.269). . <u>Acute and late toxicity:</u> No statistical difference between both groups regarding acute and late toxicity (p > 0.05).

Jin et al, 2020[77]	RCT	N=60 (tx 30, ctrl 30) **Gastric cancer**: advanced stage	HT+RT HT details were not reported	Radiotherapy alone	Survival, local control, adverse reactions	<u>Effective and local control rate:</u> Significantly higher effective and local control rates in the HT+RT versus RT alone (63.33% vs. 33.33%; p = 0.020 and 93.33% vs. 73.33%; p = 0.038, respectively). <u>Survival:</u> OS at 1, 2 and 3 years was significantly higher in the HT + RT group versus RT alone group (72.7%, 38.1%, and 10.4% vs. 51.9%, 17.3%, and 3.5% respectively, p < 0.05). Median OS was more prolonged in the HT+RT group than RT alone group (15 vs. 13 months, p = 0.040). Progression-free survival was 11 vs. 9 months, p = 0.034) in the HT+RT than the RT alone group. <u>Adverse reactions:</u> No significant difference in incidence of adverse reactions between the two groups (p > 0.05).

Safety

HT is generally a safe and well tolerated treatment when used appropriately and with current technology paired with adequate treatment planning. Toxicity in patients receiving HT with chemo-and/or radiotherapy is typically at comparable levels to that seen with cancer treatment without HT.[8] Adverse effects, contraindications, and interactions are discussed below.

Adverse Effects:

HT treatment, as monotherapy or in addition to chemotherapy and/or radiation therapy, is considered to be safe and generally well tolerated,[2,8] especially with the adoption of newer technology.[4] Advances in technology, treatment planning and availability of guidelines[16,17,208,209] since the first decade of the 21st century have improved treatment outcomes, consistency, and tolerability of treatment.[4] Safety and toxicity concerns from studies from 1970-2000 should be interpreted with caution, with an understanding that the technology and planning requirements have improved. The following side effects and adverse effects have been reported in clinical trials, observational studies, and the general literature, attributed to hyperthermia in more recent years (post-2000):

More Common (>5%):

- Discomfort during treatment[46,47,151,155]
- Mild pain[8,126,154,174]
- Local Erythema[27,154,158,159]
- Skin/superficial burn (mild-moderate; grade 1-2)[8,35,144,147]

Less common (<5%):

- Subcutaneous thermal injury/adipose burns[135,142,164]

Rare but Serious (1-4%): None Identified

Physiological Effects During and After Regional Hyperthermia:

As discussed in the mechanism of action section, LRHT has many physiological effects on the local environment including vasodilation, local physiologic hyperthermia, and increased blood flow. Although LRHT acts primarily locally, there are some documented systemic physiological changes, primarily with RHT. One study of 31 cancer patients receiving deep-regional HT with a capacitive heading device for 50 minutes to the thorax or upper abdomen evaluated changes in rectal temperature, pulse rate (PR), respiratory rate (RR), systolic and diastolic blood pressure (SBP, DBP) and percutaneous oxygen saturation (SpO2) at treatment end compared to baseline, and measured total sweat volume.[210] Over the course of the 50 minute session there were significant increases in rectal temperature (38.2 ± 1.4 vs 36.6 ± 0.8, $p < 0.001$), PR (104 ± 15 vs. 85± 16 bpm, $p < 0.05$) and RR (23 ± 3 vs. 21 ± 3/min, $p < 0.05$). Blood pressure was stable during treatment when patients were recumbent, but there was a drop in SBP and DBP with standing (SBP: 113 ± 16 vs.127 ± 18 mmHg, $p < 0.001$, DBP: 70 ± 12 vs. 75 ± 13 mmHg, $p < 0.01$). Mean SpO2 was significantly lower at 20 minutes compared to baseline (95 ± 2% vs. 97 ± 1%, $p < 0.05$), with a sustained effect over the 50-minute duration. The average sweat produced was 356 ± 173 g/m^2. This study demonstrates that there are

physiological changes that occur to cardiovascular and respiratory systems during deep regional HT, however, all are within safety limits. The authors recommend that care be taken when patients stand following treatment completion due to potential orthostatic hypotensive effects.

The authors recommend care be taken when patients stand following treatment completion due to the demonstrated orthostatic hypotensive effects.

Summary of possible systemic physiological changes associated with regional hyperthermia:

- Increased core temperature
- Increased heart rate and decreased respiratory rate
- Drop in BP on standing from recumbent position upon treatment completion
- Decrease in oxygen saturation (SpO2)
- Fluid loss through sweating

Interactions:

Chemotherapy:

HT is considered a chemo-sensitizer,[4] and is frequently combined with chemotherapy in clinical trials and observational studies (see tables 1 and 2 and clinical evidence of effectiveness for summaries of all human trials). In vitro, HT has demonstrated additive or synergistic effects with several chemotherapy agents including doxorubicin, cyclophosphamide, ifosfamide, gemcitabine, cisplatin, carboplatin, and bleomycin.[4] The means through which HT may act as a chemosensitizer is discussed in the mechanism of action section above..

While the majority of RCTs have combined HT with radiotherapy or chemoradiotherapy, a few studies have evaluated HT with chemotherapy alone.[3,97,144,205] The results have been positive for soft tissue sarcoma and gastric cancer, with improved overall survival for both, for lung cancer the results were equivocal.[97] No studies have reported a worsening of outcomes when HT is combined with chemotherapy.

Radiotherapy:

HT is considered a radiosensitizer,[4] and is frequently combined with radiotherapy in clinical trials and observational studies as discussed previously (see tables 1, 2 and clinical evidence of effectiveness for summaries of all human trials). The bulk of evidence has found the addition of HT to RT improves response rates to radiation therapy, and in some instances improves survival outcomes. A review of radiation combined with HT by Datta et al in 2015[4] found that among 1717 patients treated with radiotherapy alone and 1761 patients treated with radiotherapy with HT, the complete response rate was 39.8% for radiation alone and 54.9% for radiation paired with HT (OR 2.3, 95% CI 1.95-2.72, $p < 0.001$). The most evaluated cancer sites were breast, cervix, head and neck, rectum, urinary bladder, esophagus, and cutaneous and choroidal melanoma.

The ways in which HT may act as a radiosensitizer is discussed in the mechanism of action section above.

Targeted Therapies and Endocrine Therapies:

There is very limited research on combined use of HT with targeted therapies such as monoclonal antibodies and small molecule inhibitors, or endocrine therapies such as androgen deprivation therapy or selective

estrogen receptor modulators. A small retrospective study combined radiation with once weekly cetuximab monoclonal antibody therapy and HT in patients with locally advanced squamous cell carcinoma of the head and neck.[89] All patients achieved a complete response and there was no unacceptable toxicity. One study used HT prior to intratumoral injection of dendritic cells,[111] however this is not a commonly used treatment.

Other Medications:

LRHT should be used cautiously in patients taking medications that can alter their level of consciousness, ability to feel pain, or ability to communicate. This is to prevent the potential for more severe burns.

Other CAM Therapies:

HT has been safely administered alongside intravenous ascorbic acid (IVAA) in patients with advanced NSCLC, with potential benefit for QOL.[99,100,207] HT has been administered with hyperbaric oxygen and metabolically-supported chemotherapy in patients with NSCLC, pancreatic cancer, and gastric cancer,[80,109,132] and with hyperbaric oxygen in patients with advanced NSCLC.[110] These studies found that treatments were well tolerated with no serious adverse events. HT has been combined with Traditional Chinese Herbal Medicine and intraperitoneal chemotherapy with good outcomes in patients with peritoneal tumors.[174] An observational study compared the use of HT, Boswellia caterii, mistletoe and selenium in patients with glioblastoma receiving temozolomide to temozolomide alone.[22] There was no significant difference in mean survival, however, fewer grade III-IV adverse events were experienced in the combined treatment arm. Lastly, HT with an immune modulator called Biobran (MGN-3-Arabinoxylane) was combined for chronic fatigue in people with a history of cancer, and fatigue was reduced compared to control after 6 months.[206]

Cautions and Contraindications:

Cautions and contraindications may vary by hyperthermia device; common contraindications include:[211,212]

- Patients with implanted/worn/carried medical devices, implants, or any foreign objects (e.g., pacemakers, implanted defibrillators, insulin pumps, metallic implant, silicon breast implants, implanted hearing aids, prosthetics)
- Inability to feel or respond to pain, including sedation, loss of consciousness, and severe neuropathy
- Systemic fever >38°C[17]
- Severe pulmonary disease (FEV <50%)
- Cardiovascular high-risk patients (unstable angina, imminent threat of infarction, MI < 6 months ago, cardiac decompensation requiring medication, arrythmia requiring medication, heart rate > 90 bpm, diastolic hypertension > 100 mmHg and/or systolic hypertension > 180 mmHg while on medication, diastolic hypotension < 50 mmHg and/or systolic hypotension < 90 mmHg). Severe cerebrovascular disease (multiple CVA and/or CVA < 6 months ago)
- Treatment delivered to areas of prior irradiation
- Known decreased circulation in heated area (vasoconstrictive drugs, DIC, ischemia, etc.)

- Patient is prone to hemorrhage, has the presence of an open wound and/or has had a recent surgery
- Patient with organ transplant
- Children (due to lack of evidence)

Practical Aspects of Hyperthermia Treatment

A detailed discussion of the technical requirements to perform effective and safe LRHT is beyond the scope of this monograph, however a general overview of pertinent details is discussed. Quality assurance guidelines for both superficial[16,208] and deep regional HT[17,209] have been published with the goals of ensuring a minimum quality standard for treatment and methods for clinical research. The first regional HT guideline was published in 1998[209] and a partial update in 2011,[17] and the superficial HT guidelines in 2017.[16,208] These can be reviewed along with manufacturer requirements for further details on treatment planning and application.

The effectiveness of HT likely depends on the ability to achieve the appropriate temperature for the required duration (known as the thermal dose) without negatively affecting healthy tissue.[16] Given the clear thermal dose-effect relationship,[213] the technical capabilities of the device as well as the treatment planning are of high importance.

Treatment Planning and Monitoring:

Treatment planning is essential for safe and effective HT treatment.[213] The tumor must be localized using CT or MRI imaging and the clinician must determine if it's safe and feasible for the patient to be treated.[17,209] The treatment plan is created including the tumor target temperature, maximum temperatures, starting power and upper limit of power, treatment duration, and number of treatments.[209]

During treatment, there should be monitoring of the temperature (normal tissue, tumor tissue, and systemic temperature), vitals (such as heart rate and blood pressure), and documentation of patient and treatment details, including any side effects.[209]

Treatment Team:

Performing HT will usually require a clinician (physician or otherwise qualified healthcare provider), physicists/engineers to manage the physical and technical aspects of a HT machine, and technicians and/or nurses who can administer treatment under the supervision of the clinician.[16]

Timing with Other Cancer Therapies:

HT is primarily used in conjunction with conventional treatments such as chemotherapy and radiation therapy, thus timing and coordination are important considerations. Synergistic effects appear to rely heavily on time intervals between HT and adjunctive treatments, with concurrent or close application producing greater response than spaced out regimens.[1] This may be at least partially due to oxygenation and tissue perfusion induced by HT. While some studies have reported increases lasting up to 48 hours, the majority of studies have found that the tissue oxygenation rapidly returns back to normal.[11]

Timing with chemotherapy:

Quality assurance guidelines for HT state that chemotherapy be given just before or simultaneous to HT.[16] RCTs of HT with chemotherapy generally administer heating the same day as chemotherapy following the treatment (often within 1-hour of treatment completion),[32,97,144] or during the chemotherapy infusion.[75]

Timing with radiation therapy:

Quality assurance guidelines for HT state that radiation be given ideally within 1 hour of HT (but up to 4 hours is acceptable), and if technically feasible they can be done together.[16] The interval of time between HT treatment and radiation therapy has been associated with recurrence risk and overall survival.[8] Shorter intervals of time between these two treatments are associated with improvements in survival.

RCTs of HT with radiotherapy most often administer HT immediately following radiation (within minutes to 2 hours),[25,30,32,76,81,112,164] but some have administered treatment immediately prior to radiation.[33,214]

Treatment Temperature:

The target tumor temperature range for locoregional hyperthermia can range from 39-45°C,[4] however, 41-43°C is considered optimal.[4,213] RCTs summarized in table 2 targeted temperatures ranging from 39°C-43°C, with 42-43 degrees being most common. A guideline for regional HT quality assurance recommends that temperature remain below 43°C in normal tissue, and not exceed 44°C in target tumor tissue.[17] Irreversible tissue damage and necrosis can occur at temperatures of 44-46°C.[17] If measured, temperature is usually monitored by minimally invasive thermometry probes.[213]

Treatment Time:

The current guideline for hyperthermia treatment time is to allow up to 30 minutes for target temperature to be reached, followed by 60 minutes at target temperature.[17]

Based on existing clinical studies, HT duration is sometimes specified as the time at target tumor temperature (e.g. 30-60 minutes once target temperature is achieved), and other times a flat duration regardless of tumor temperature (e.g. 1 hour). In RCTs reported on in table 2, heating durations ranged from 20-60 minutes once target temperature was achieved, or up to 70 minutes total duration; the most frequently used duration was 60 minutes.

Treatment Frequency and Duration of Use:

RCTs summarized in table 2 used HT ranging from daily during short-term radiation (<1 week) to once weekly, with the most common protocol being 1-2 treatments per week. Duration of use is typically for the duration of the conventional treatment (e.g. chemotherapy and/or radiotherapy), which often corresponds to 3-12 weeks.

Power:

Power varies by the heating mechanism and device used.

Devices and Technology:

Devices must be capable of delivering controlled heat at a predetermined level to the tumor with minimal heating of surrounding tissue. Devices must be capable of

increasing tumor temperature to 40-43°C for 60 minutes.[17]

Several different HT devices have been used in studies for cancer. The most commonly used devices include the BSD 1000 and 2000, Thermotron RF-8, and Oncotherm EHY 2000+ and 3010. The BSD devices are radiofrequency powered and can use various annular phased array applicators, the oncotherm EHY are capacitive heating devices using modulated radiofrequency (also known as modulated electro-hyperthermia (mEHT)), and the Thermotron RF-8 is a radiofrequency capacitive device.[215]

Availability and Cost of Treatment in Canada:

LRHT is generally provided in private clinics by complementary and integrative health care providers. Research is ongoing, but LRHT is not considered standard of care for cancer management at this time. Treatments are not available in all parts of Canada; there are clinics offering this treatment in British Columbia, Alberta, Manitoba, and Ontario. The cost of LRHT typically ranges from $300-400 per treatment based on internet searches and fees charged by Canadian clinics offering LRHT.

Disclaimer

This monograph provides a summary of available evidence and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

References

1. Behrouzkia Z, Joveini Z, Keshavarzi B, Eyvazzadeh N, Aghdam RZ. Hyperthermia: How Can It Be Used? *Oman Med J*. Mar 2016;31(2):89-97. doi:10.5001/omj.2016.19
2. 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
3. Issels RD, Lindner LH, Verweij J, 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. Clinical Trial, Phase III; Journal Article; Multicenter Study; Randomized Controlled Trial. *JAMA oncology*. 2018;4(4):483-492. doi:10.1001/jamaoncol.2017.4996
4. Datta NR, Ordóñez SG, Gaipl US, et al. Local hyperthermia combined with radiotherapy and-/or chemotherapy: recent advances and promises for the future. *Cancer Treat Rev*. Nov 2015;41(9):742-53. doi:10.1016/j.ctrv.2015.05.009
5. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. *Lancet Oncol*. Aug 2002;3(8):487-97. doi:10.1016/s1470-2045(02)00818-5
6. Cheng Y, Weng S, Yu L, Zhu N, Yang M, Yuan Y. The Role of Hyperthermia in the Multidisciplinary Treatment of Malignant Tumors. *Integrative cancer therapies*. Jan-Dec 2019;18:1534735419876345. doi:10.1177/1534735419876345
7. Hoekstra HJ, van Ginkel RJ. Hyperthermic isolated limb perfusion in the management of extremity sarcoma. *Current opinion in oncology*. Jul 2003;15(4):300-3. doi:10.1097/00001622-200307000-00004
8. Fiorentini G, Sarti D, Gadaleta CD, et al. A Narrative Review of Regional Hyperthermia: Updates From 2010 to 2019. *Integr Cancer Ther*. Jan-Dec 2020;19:1534735420932648. doi:10.1177/1534735420932648
9. Zhu L, Altman MB, Laszlo A, et al. Ultrasound Hyperthermia Technology for Radiosensitization. *Ultrasound Med Biol*. May 2019;45(5):1025-1043. doi:10.1016/j.ultrasmedbio.2018.12.007
10. Datta NR, Kok HP, Crezee H, Gaipl US, Bodis S. Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses. *Front Oncol*. 2020;10:819. doi:10.3389/fonc.2020.00819
11. Vaupel PW, Kelleher DK. Pathophysiological and vascular characteristics of tumours and their importance for hyperthermia: heterogeneity is the key issue. *Int J Hyperthermia*. 2010;26(3):211-23. doi:10.3109/02656731003596259
12. Issels RD. Hyperthermia adds to chemotherapy. *Eur J Cancer*. Nov 2008;44(17):2546-54. doi:10.1016/j.ejca.2008.07.038
13. Skitzki JJ, Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. *Curr Opin Investig Drugs*. Jun 2009;10(6):550-8.
14. Minnaar CA, Kotzen JA, Ayeni OA, Vangu MD, Baeyens A. Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients. *Front Oncol*. 2020;10:376. doi:10.3389/fonc.2020.00376
15. Issels R, Kampmann E, Kanaar R, Lindner LH. Hallmarks of hyperthermia in driving the future of clinical hyperthermia as targeted therapy: translation into clinical application. *Int J Hyperthermia*. 2016;32(1):89-95. doi:10.3109/02656736.2015.1119317
16. Trefná HD, Crezee H, Schmidt M, et al. Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements. *Int J Hyperthermia*. Jun 2017;33(4):471-482. doi:10.1080/02656736.2016.1277791
17. Bruggmoser G, Bauchowitz S, Canters R, et al. Quality assurance for clinical studies in regional deep hyperthermia. *Strahlenther Onkol*. Oct 2011;187(10):605-10. doi:10.1007/s00066-011-1145-x
18. Longo TA, Gopalakrishna A, Tsivian M, et al. A systematic review of regional hyperthermia therapy in bladder cancer. *Int J Hyperthermia*. Jun 2016;32(4):381-9. doi:10.3109/02656736.2016.1157903

19. 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
20. Datta NR, Eberle B, Puric E, et al. Is hyperthermia combined with radiotherapy adequate in elderly patients with muscle-invasive bladder cancers? Thermo-radiobiological implications from an audit of initial results. *Int J Hyperthermia*. Jun 2016;32(4):390-7. doi:10.3109/02656736.2015.1132340
21. Merten R, Ott O, Haderlein M, et al. Long-Term Experience of Chemoradiotherapy Combined with Deep Regional Hyperthermia for Organ Preservation in High-Risk Bladder Cancer (Ta, Tis, T1, T2). *Oncologist*. Dec 2019;24(12):e1341-e1350. doi:10.1634/theoncologist.2018-0280
22. 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*. Nov 3 2017;7(11):e017387. doi:10.1136/bmjopen-2017-017387
23. 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*. Jan-Dec 2019;18:1534735418812691. doi:10.1177/1534735418812691
24. Wismeth C, Dudel C, Pascher C, et al. Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas: phase I clinical results. *J Neurooncol*. Jul 2010;98(3):395-405. doi:10.1007/s11060-009-0093-0
25. 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*. Apr 1 2016;94(5):1073-87. doi:10.1016/j.ijrobp.2015.12.361
26. Zagar TM, Vujaskovic Z, Formenti S, et al. Two phase I dose-escalation/pharmacokinetics studies of low temperature liposomal doxorubicin (LTLD) and mild local hyperthermia in heavily pretreated patients with local regionally recurrent breast cancer. *Int J Hyperthermia*. Aug 2014;30(5):285-94. doi:10.3109/02656736.2014.936049
27. Zoul Z, Filip S, Melichar B, Dvorák J, Odrázka K, Petera J. Weekly paclitaxel combined with local hyperthermia in the therapy of breast cancer locally recurrent after mastectomy--a pilot experience. *Onkologie*. Aug 2004;27(4):385-8. doi:10.1159/000079093
28. Stoetzer O, Di Gioia D, Issels RD, et al. Post-Neoadjuvant Gemcitabine and Cisplatin with Regional Hyperthermia for Patients with Triple-Negative Breast Cancer and Non-pCR after Neoadjuvant Chemotherapy: A Single-Institute Experience. *Breast Care (Basel)*. Apr 2021;16(2):173-180. doi:10.1159/000507473
29. Nagata T, Kanamori M, Sekine S, Arai M, Moriyama M, Fujii T. Clinical study of modulated electro-hyperthermia for advanced metastatic breast cancer. *Mol Clin Oncol*. May 2021;14(5):103. doi:10.3892/mco.2021.2265
30. 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*. Nov 2016;32(7):809-21. doi:10.1080/02656736.2016.1195924
31. Lutgens L, van der Zee J, Pijls-Johannesma M, et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *The Cochrane database of systematic reviews*. Mar 17 2010;(3):Cd006377. doi:10.1002/14651858.CD006377.pub3
32. 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*. Nov 2016;32(7):801-8. doi:10.1080/02656736.2016.1213430
33. 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(6):e0217894. doi:10.1371/journal.pone.0217894
34. 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*. Jul 2017;14(1):73-78. doi:10.3892/ol.2017.6117

35. Minnaar CA, Kotzen JA, Naidoo T, et al. Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients. *Int J Hyperthermia*. 2020;37(1):263-272. doi:10.1080/02656736.2020.1737253
36. Wang Y, Hong W, Che S, et al. Outcomes for Hyperthermia Combined with Concurrent Radiochemotherapy for Patients with Cervical Cancer. Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't. *International journal of radiation oncology, biology, physics*. 2020;107(3):499-511. doi:10.1016/j.ijrobp.2020.03.006
37. 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)*. Jan 27 2022;14(3)doi:10.3390/cancers14030656
38. de Wit R, van der Zee J, van der Burg ME, et al. A phase I/II study of combined weekly systemic cisplatin and locoregional hyperthermia in patients with previously irradiated recurrent carcinoma of the uterine cervix. *Br J Cancer*. Jul 1999;80(9):1387-91. doi:10.1038/sj.bjc.6690533
39. Dinges S, Harder C, Wurm R, et al. Combined treatment of inoperable carcinomas of the uterine cervix with radiotherapy and regional hyperthermia. Results of a phase II trial. *Strahlenther Onkol*. Oct 1998;174(10):517-21. doi:10.1007/bf03038984
40. Rietbroek RC, Schilthuis MS, Bakker PJ, et al. Phase II trial of weekly locoregional hyperthermia and cisplatin in patients with a previously irradiated recurrent carcinoma of the uterine cervix. *Cancer*. Mar 1 1997;79(5):935-43. doi:10.1002/(sici)1097-0142(19970301)79:5<935::aid-cncr10>3.0.co;2-3
41. 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(6):549-53. doi:10.3109/02656736.2012.673047
42. Franckena M, De Wit R, Ansink AC, et al. Weekly systemic cisplatin plus locoregional hyperthermia: an effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area. *Int J Hyperthermia*. Aug 2007;23(5):443-50. doi:10.1080/02656730701549359
43. Westermann AM, Jones EL, Schem BC, et al. First results of triple-modality treatment combining radiotherapy, chemotherapy, and hyperthermia for the treatment of patients with stage IIB, III, and IVA cervical carcinoma. *Cancer*. Aug 15 2005;104(4):763-70. doi:10.1002/cncr.21128
44. Asao T, Sakurai H, Harashima K, et al. The synchronization of chemotherapy to circadian rhythms and irradiation in pre-operative chemoradiation therapy with hyperthermia for local advanced rectal cancer. *Int J Hyperthermia*. Aug 2006;22(5):399-406. doi:10.1080/02656730600799873
45. Barsukov YA, Gordeyev SS, Tkachev SI, Fedyanin MY, Perevoshikov AG. Phase II study of concomitant chemoradiotherapy with local hyperthermia and metronidazole for locally advanced fixed rectal cancer. *Colorectal Dis*. Sep 2013;15(9):1107-14. doi:10.1111/codi.12281
46. 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(2):108-17. doi:10.3109/02656730903333958
47. Milani V, Pazos M, Issels RD, et al. Radiochemotherapy in combination with regional hyperthermia in preirradiated patients with recurrent rectal cancer. *Strahlenther Onkol*. Mar 2008;184(3):163-8. doi:10.1007/s00066-008-1731-8
48. Rau B, Wust P, Hohenberger P, et al. Preoperative hyperthermia combined with radiochemotherapy in locally advanced rectal cancer: a phase II clinical trial. *Ann Surg*. Mar 1998;227(3):380-9. doi:10.1097/00000658-199803000-00010
49. Rau B, Wust P, Tilly W, et al. Preoperative radiochemotherapy in locally advanced or recurrent rectal cancer: regional radiofrequency hyperthermia correlates with clinical parameters. *Int J Radiat Oncol Biol Phys*. Sep 1 2000;48(2):381-91. doi:10.1016/s0360-3016(00)00650-7
50. Riess H, Löffel J, Wust P, et al. A pilot study of a new therapeutic approach in the treatment of locally advanced stages of rectal cancer: neoadjuvant radiation, chemotherapy and regional hyperthermia. *Eur J Cancer*. Jul-Aug 1995;31a(7-8):1356-60. doi:10.1016/0959-8049(95)00178-l
51. Wust P, Rau B, Gellerman J, et al. Radiochemotherapy and hyperthermia in the treatment of rectal cancer. *Recent Results Cancer Res*. 1998;146:175-91. doi:10.1007/978-3-642-71967-7_16

52. You SH, Kim S. Feasibility of modulated electro-hyperthermia in preoperative treatment for locally-advanced rectal cancer: Early phase 2 clinical results. *Neoplasma*. Feb 9 2020;doi:10.4149/neo_2020_190623N538
53. Ott OJ, Gani C, Lindner LH, et al. Neoadjuvant Chemoradiation Combined with Regional Hyperthermia in Locally Advanced or Recurrent Rectal Cancer. *Cancers (Basel)*. Mar 13 2021;13(6)doi:10.3390/cancers13061279
54. Schem BC, Pfeffer F, Ott MA, et al. Long-Term Outcome in a Phase II Study of Regional Hyperthermia Added to Preoperative Radiochemotherapy in Locally Advanced and Recurrent Rectal Adenocarcinomas. *Cancers (Basel)*. Jan 29 2022;14(3)doi:10.3390/cancers14030705
55. Lee Y, Kim S, Cha H, et al. Long-Term Feasibility of 13.56 MHz Modulated Electro-Hyperthermia-Based Preoperative Thermoradiochemotherapy in Locally Advanced Rectal Cancer. *Cancers (Basel)*. Mar 1 2022;14(5)doi:10.3390/cancers14051271
56. Gani C, Lamprecht U, Ziegler A, et al. Deep regional hyperthermia with preoperative radiochemotherapy in locally advanced rectal cancer, a prospective phase II trial. *Radiother Oncol*. Jun 2021;159:155-160. doi:10.1016/j.radonc.2021.03.011
57. 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(2):187-92. doi:10.3109/02656736.2015.1117661
58. Schaffer M, Krych M, Pachmann S, et al. Feasibility and morbidity of combined hyperthermia and radiochemotherapy in recurrent rectal cancer--preliminary results. *Onkologie*. Apr 2003;26(2):120-4. doi:10.1159/000069830
59. 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(8):707-14. doi:10.3109/02656736.2012.722263
60. Shoji H, Motegi M, Osawa K, et al. A novel strategy of radiofrequency hyperthermia (neothermia) in combination with preoperative chemoradiotherapy for the treatment of advanced rectal cancer: a pilot study. *Cancer Med*. Jun 2015;4(6):834-43. doi:10.1002/cam4.431
61. Tsutsumi S, Tabe Y, Fujii T, et al. Tumor response and negative distal resection margins of rectal cancer after hyperthermochemoradiation therapy. *Anticancer Res*. Nov 2011;31(11):3963-7.
62. Wang Y, Lu S, Shao Y, et al. Deep regional hyperthermia combined with modern concurrent chemoradiotherapy increases T-downstaging rate in locally advanced rectal cancer. *Int J Hyperthermia*. 2022;39(1):431-436. doi:10.1080/02656736.2022.2044077
63. Kim S, Lee JH, Cha J, You SH. Beneficial effects of modulated electro-hyperthermia during neoadjuvant treatment for locally advanced rectal cancer. *Int J Hyperthermia*. 2021;38(1):144-151. doi:10.1080/02656736.2021.1877837
64. Ohguri T, Imada H, Kato F, et al. Radiotherapy with 8 MHz radiofrequency-capacitive regional hyperthermia for pain relief of unresectable and recurrent colorectal cancer. *Int J Hyperthermia*. Feb 2006;22(1):1-14. doi:10.1080/02656730500381152
65. 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*. Mar 2016;34(1):34-44. doi:10.3857/roj.2016.34.1.34
66. González González D, van Dijk JD, Blank LE. Radiotherapy and hyperthermia. *Eur J Cancer*. Jul-Aug 1995;31a(7-8):1351-5. doi:10.1016/0959-8049(95)00177-k
67. Ott OJ, Schmidt M, Semrau S, et al. Chemoradiotherapy with and without deep regional hyperthermia for squamous cell carcinoma of the anus. *Strahlenther Onkol*. Jul 2019;195(7):607-614. Radiochemotherapie mit und ohne regionale Tiefenhyperthermie bei Plattenepithelkarzinomen des Anus. doi:10.1007/s00066-018-1396-x
68. 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*. Apr 2017;42(2):155-164. doi:10.1111/jcpt.12498
69. Hulshof MC, Van Haaren PM, Van Lanschot JJ, et al. Preoperative chemoradiation combined with regional hyperthermia for patients with resectable esophageal cancer. *Int J Hyperthermia*. Feb 2009;25(1):79-85. doi:10.1080/02656730802464078

70. Albregts M, Hulshof MC, Zum Vörde Sive Vörding PJ, et al. A feasibility study in oesophageal carcinoma using deep loco-regional hyperthermia combined with concurrent chemotherapy followed by surgery. *Int J Hyperthermia*. Sep 2004;20(6):647-59. doi:10.1080/02656730410001714977
71. Sheng L, Ji Y, Wu Q, Du X. Regional hyperthermia combined with radiotherapy for esophageal squamous cell carcinoma with supraclavicular lymph node metastasis. *Oncotarget*. Jan 17 2017;8(3):5339-5348. doi:10.18632/oncotarget.14148
72. Kitamura K, Kuwano H, Watanabe M, et al. Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. *J Surg Oncol*. Sep 1995;60(1):55-8. doi:10.1002/jso.2930600111
73. Nozoe T, Kuwano H, Watanabe M, et al. The long-term results of pre-operative hyperthermo-chemo-radiotherapy for oesophageal carcinoma--a comparison with preoperative radiation therapy alone. *Eur J Surg Oncol*. Aug 1995;21(4):374-8. doi:10.1016/s0748-7983(95)92417-5
74. Sugimachi K, Kitamura K, Baba K, et al. Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus--a prospective randomized trial. *Int J Hyperthermia*. May-Jun 1992;8(3):289-95. doi:10.3109/02656739209021783
75. Fang H, Zhang Y, Wu Z, et al. Regional Hyperthermia Combined with Chemotherapy in Advanced Gastric Cancer. *Open Med (Wars)*. 2019;14:85-90. doi:10.1515/med-2019-0012
76. Shchepotin IB, Evans SR, Chorny V, et al. Intensive preoperative radiotherapy with local hyperthermia for the treatment of gastric carcinoma. *Surg Oncol*. Feb 1994;3(1):37-44. doi:10.1016/0960-7404(94)90022-1
77. Jin X, Qi Q, Wang Y, Fan L, Huo Z. The Efficacy of Hyperthermia Combined with Radiotherapy in the Treatment of Advanced Gastric Cancer. Journal: Article. *Anti-tumor pharmacy*. 2020;10(3):320-323. doi:10.3969/j.issn.2095-1264.2020.03.10
78. Minakuchi H, Hirayama R, Sawai S, et al. Clinical trials of long-term RF local hyperthermia for advanced gastric cancer. *Jpn J Surg*. Mar 1990;20(2):238-9. doi:10.1007/bf02470777
79. Zhu L, Xu Y, Shan Y, Zheng R, Wu Z, Ma S. Intraperitoneal perfusion chemotherapy and whole abdominal hyperthermia using external radiofrequency following radical D2 resection for treatment of advanced gastric cancer. *Int J Hyperthermia*. 2019;36(1):403-407. doi:10.1080/02656736.2019.1579372
80. Iyikesici MS. Survival outcomes of metabolically supported chemotherapy combined with ketogenic diet, hyperthermia, and hyperbaric oxygen therapy in advanced gastric cancer. *Niger J Clin Pract*. May 2020;23(5):734-740. doi:10.4103/njcp.njcp_509_18
81. Datta NR, Rogers S, Ordóñez 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(1):31-40. doi:10.3109/02656736.2015.1099746
82. Arcangeli G, Cividalli A, Mauro F, Nervi C, Pavin G. Enhanced effectiveness of adriamycin and bleomycin combined with local hyperthermia in neck node metastases from head and neck cancers. *Tumori*. Aug 31 1979;65(4):481-6.
83. Amichetti M, Romano M, Busana L, et al. Hyperfractionated radiation in combination with local hyperthermia in the treatment of advanced squamous cell carcinoma of the head and neck: a phase I-II study. *Radiother Oncol*. Nov 1997;45(2):155-8. doi:10.1016/s0167-8140(97)00134-5
84. Gabriele P, Amichetti M, Orecchia R, Valdagni R. Hyperthermia and radiation therapy for inoperable or recurrent parotid carcinoma. A phase I/II study. *Cancer*. Feb 15 1995;75(4):908-13. doi:10.1002/1097-0142(19950215)75:4<908::aid-cncr2820750403>3.0.co;2-z
85. Serin M, Erkal HS, Cakmak A. Radiation therapy, cisplatin and hyperthermia in combination in management of patients with carcinomas of the head and neck with N2 or N3 metastatic cervical lymph nodes. *Radiother Oncol*. Jan 1999;50(1):103-6. doi:10.1016/s0167-8140(98)00098-x
86. Serin M, Erkal HS, Cakmak A. Radiation therapy, cisplatin and hyperthermia in combination in management of patients with recurrent carcinomas of the head and neck with metastatic cervical lymph nodes. *Int J Hyperthermia*. Sep-Oct 1999;15(5):371-81. doi:10.1080/026567399285567
87. Chang P, Sapozink MD, Grunberg SM, et al. Unresectable primary and recurrent head and neck tumors: effect of hyperthermia and carboplatin--preliminary experience. *Radiology*. Mar 2000;214(3):688-92. doi:10.1148/radiology.214.3.r00mr51688

88. Huilgol NG, Gupta S, Dixit R. Chemoradiation with hyperthermia in the treatment of head and neck cancer. *Int J Hyperthermia*. Feb 2010;26(1):21-5. doi:10.3109/02656730903418283
89. Huilgol NG. A retrospective analysis of patients with head and neck cancer treated with radiation, hyperthermia, and cetuximab: A brief report of outcome. *J Cancer Res Ther*. Jul-Sep 2016;12(3):1164-1166. doi:10.4103/0973-1482.194600
90. Liang XH, He YW, Tang YL, et al. Thermochemotherapy of lower lip squamous cell carcinoma without metastases: an experience of 31 cases. *J Craniomaxillofac Surg*. Jun 2010;38(4):260-5. doi:10.1016/j.jcms.2009.07.008
91. Amichetti M, Graiff C, Fellin G, et al. Cisplatin, hyperthermia, and radiation (trimodal therapy) in patients with locally advanced head and neck tumors: a phase I-II study. *Int J Radiat Oncol Biol Phys*. Aug 1 1993;26(5):801-7. doi:10.1016/0360-3016(93)90495-h
92. Akuta K, Abe M, Kondo M, et al. Combined effects of hepatic arterial embolization using degradable starch microspheres (DSM) in hyperthermia for liver cancer. *Int J Hyperthermia*. Mar-Apr 1991;7(2):231-42. doi:10.3109/02656739109004993
93. Tanaka Y, Yamamoto K, Murata T, Nagata K. Effects of multimodal treatment and hyperthermia on hepatic tumors. *Cancer Chemother Pharmacol*. 1992;31 Suppl:S111-4. doi:10.1007/bf00687119
94. Ge H, Huang J. Regional hyperthermia in the treatment of primary hepatic carcinoma. *J Surg Oncol*. Jul 2000;74(3):193-5. doi:10.1002/1096-9098(200007)74:3<193::aid-jso5>3.0.co;2-2
95. Kamisawa T, Tu Y, Egawa N, et al. Thermo-chemo-radiotherapy for advanced bile duct carcinoma. *World J Gastroenterol*. Jul 21 2005;11(27):4206-9. doi:10.3748/wjg.v11.i27.4206
96. Petersen IA, Kapp DS. Local hyperthermia and radiation therapy in the retreatment of superficially located recurrences in Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. Mar 1990;18(3):603-11. doi:10.1016/0360-3016(90)90067-t
97. 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(1):27-32. doi:10.3109/02656736.2010.500645
98. Mitsumori M, Zeng ZF, Oliynychenko P, 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*. Jun 2007;12(3):192-8. doi:10.1007/s10147-006-0647-5
99. Ou J, Zhu X, Lu Y, et al. The safety and pharmacokinetics of high dose intravenous ascorbic acid synergy with modulated electrohyperthermia in Chinese patients with stage III-IV non-small cell lung cancer. Clinical Trial, Phase I; Journal Article; Randomized Controlled Trial. *European journal of pharmaceutical sciences*. 2017;109:412-418. doi:10.1016/j.ejps.2017.08.011
100. Ou J, Zhu X, Chen P, et al. A randomized phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer. *J Adv Res*. Jul 2020;24:175-182. doi:10.1016/j.jare.2020.03.004
101. Jiang Z, Yan W, Ming J, Yu Y. Docetaxel weekly regimen in conjunction with RF hyperthermia for pretreated locally advanced non-small cell lung cancer: a preliminary study. *BMC Cancer*. Oct 6 2007;7:189. doi:10.1186/1471-2407-7-189
102. Sakurai H, Hayakawa K, Mitsuhashi N, et al. Effect of hyperthermia combined with external radiation therapy in primary non-small cell lung cancer with direct bony invasion. *Int J Hyperthermia*. Sep-Oct 2002;18(5):472-83. doi:10.1080/02656730210146917
103. Karasawa K, Muta N, Nakagawa K, et al. Thermoradiotherapy in the treatment of locally advanced nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys*. Dec 1 1994;30(5):1171-7. doi:10.1016/0360-3016(94)90325-5
104. Ohguri T, Imada H, Yahara K, et al. Re-irradiation plus regional hyperthermia for recurrent non-small cell lung cancer: a potential modality for inducing long-term survival in selected patients. *Lung Cancer*. Jul 2012;77(1):140-5. doi:10.1016/j.lungcan.2012.02.018
105. Ohguri T, Imada H, Yahara K, et al. Radiotherapy with 8-MHz radiofrequency-capacitive regional hyperthermia for stage III non-small-cell lung cancer: the radiofrequency-output power correlates with the intraesophageal temperature and clinical outcomes. *Int J Radiat Oncol Biol Phys*. Jan 1 2009;73(1):128-35. doi:10.1016/j.ijrobp.2008.03.059

106. Kim YP, Choi Y, Kim S, et al. Conventional cancer treatment alone or with regional hyperthermia for pain relief in lung cancer: A case-control study. *Complement Ther Med*. Jun 2015;23(3):381-7. doi:10.1016/j.ctim.2015.04.004
107. de Graaf-Strukowska L, van der Zee J, van Putten W, Senan S. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura--a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys*. Feb 1 1999;43(3):511-6. doi:10.1016/s0360-3016(98)00409-x
108. Moon SD, Ohguri T, Imada H, et al. Definitive radiotherapy plus regional hyperthermia with or without chemotherapy for superior sulcus tumors: a 20-year, single center experience. *Lung Cancer*. Mar 2011;71(3):338-43. doi:10.1016/j.lungcan.2010.06.007
109. Iyikesici MS. Feasibility study of metabolically supported chemotherapy with weekly carboplatin/paclitaxel combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy in metastatic non-small cell lung cancer. *Int J Hyperthermia*. 2019;36(1):446-455. doi:10.1080/02656736.2019.1589584
110. Ohguri T, Imada H, Narisada H, et al. Systemic chemotherapy using paclitaxel and carboplatin plus regional hyperthermia and hyperbaric oxygen treatment for non-small cell lung cancer with multiple pulmonary metastases: preliminary results. *Int J Hyperthermia*. Mar 2009;25(2):160-7. doi:10.1080/02656730802610357
111. Guo J, Zhu J, Sheng X, et al. Intratumoral injection of dendritic cells in combination with local hyperthermia induces systemic antitumor effect in patients with advanced melanoma. Journal Article; Randomized Controlled Trial; Research Support, Non-U.S. Gov't. *International journal of cancer*. 2007;120(11):2418-2425. doi:10.1002/ijc.22551
112. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. *Lancet*. Mar 4 1995;345(8949):540-3. doi:10.1016/s0140-6736(95)90463-8
113. Di Filippo F, Carlini S, Garinei R, et al. Local hyperthermia and systemic chemotherapy for treatment of recurrent melanoma. *World J Surg*. May-Jun 1995;19(3):359-62. doi:10.1007/bf00299158
114. Shidnia H, Hornback NB, Shen RN, Shupe RE, Yune M. An overview of the role of radiation therapy and hyperthermia in treatment of malignant melanoma. *Adv Exp Med Biol*. 1990;267:531-45. doi:10.1007/978-1-4684-5766-7_58
115. Ben-Yosef R, Kapp DS. Prognostic factors in metastatic malignant melanoma treated with combined radiation therapy and hyperthermia. *Int J Hyperthermia*. Nov-Dec 1993;9(6):767-81. doi:10.3109/02656739309034980
116. Richtig E, Hoff M, Rehak P, et al. Efficacy of superficial and deep regional hyperthermia combined with systemic chemotherapy and radiotherapy in metastatic melanoma. *J Dtsch Dermatol Ges*. Aug 2003;1(8):635-42. doi:10.1046/j.1610-0387.2003.03719.x
117. Leopold KA, Oleson JR, Clarke-Pearson D, et al. Intraperitoneal cisplatin and regional hyperthermia for ovarian carcinoma. *Int J Radiat Oncol Biol Phys*. Dec 1 1993;27(5):1245-51. doi:10.1016/0360-3016(93)90550-f
118. Alvarez Secord A, Jones EL, Hahn CA, et al. Phase I/II trial of intravenous Doxil and whole abdomen hyperthermia in patients with refractory ovarian cancer. *Int J Hyperthermia*. Jun 2005;21(4):333-47. doi:10.1080/02656730500110155
119. Hahn CA, Jones EL, Blivin JL, et al. Prospective assessment of quality of life in ovarian cancer patients receiving whole abdomen hyperthermia and liposomal doxorubicin. *Int J Hyperthermia*. Jun 2005;21(4):349-57. doi:10.1080/02656730400022260
120. Fotopoulou C, Cho CH, Kraetschell R, et al. Regional abdominal hyperthermia combined with systemic chemotherapy for the treatment of patients with ovarian cancer relapse: Results of a pilot study. *Int J Hyperthermia*. 2010;26(2):118-26. doi:10.3109/02656730903369200
121. Formenti SC, Shrivastava PN, Sapozink M, et al. Abdomino-pelvic hyperthermia and intraperitoneal carboplatin in epithelial ovarian cancer: feasibility, tolerance and pharmacology. *Int J Radiat Oncol Biol Phys*. Jul 15 1996;35(5):993-1001. doi:10.1016/0360-3016(96)00092-2
122. Jones E, Alvarez Secord A, Prosnitz LR, et al. Intra-peritoneal cisplatin and whole abdomen hyperthermia for relapsed ovarian carcinoma. *Int J Hyperthermia*. Mar 2006;22(2):161-72. doi:10.1080/02656730500515270
123. Yoo HJ, Lim MC, Seo SS, Kang S, Joo J, Park SY. Phase I/II clinical trial of modulated electro-hyperthermia treatment in patients with relapsed, refractory or progressive heavily treated ovarian cancer. *Jpn J Clin Oncol*. Sep 1 2019;49(9):832-838. doi:10.1093/jjco/hyz071

124. Ishikawa T, Kokura S, Sakamoto N, et al. Phase II trial of combined regional hyperthermia and gemcitabine for locally advanced or metastatic pancreatic cancer. *Int J Hyperthermia*. 2012;28(7):597-604. doi:10.3109/02656736.2012.695428
125. He M, Sun J, Zhao D, et al. Modified-FOLFIRINOX combined with deep regional hyperthermia in pancreatic cancer: a retrospective study in Chinese patients. *Int J Hyperthermia*. 2019;36(1):394-402. doi:10.1080/02656736.2019.1579371
126. Tschoep-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(1):8-16. doi:10.3109/02656736.2012.740764
127. 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*. Oct 2011;187(10):619-25. doi:10.1007/s00066-011-2226-6
128. Ohguri T, Imada H, Yahara K, et al. Concurrent chemoradiotherapy with gemcitabine plus regional hyperthermia for locally advanced pancreatic carcinoma: initial experience. *Radiat Med*. Dec 2008;26(10):587-96. doi:10.1007/s11604-008-0279-y
129. Maebayashi T, Ishibashi N, Aizawa T, et al. Treatment outcomes of concurrent hyperthermia and chemoradiotherapy for pancreatic cancer: Insights into the significance of hyperthermia treatment. *Oncol Lett*. Jun 2017;13(6):4959-4964. doi:10.3892/ol.2017.6066
130. 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*. Jan-Dec 2019;18:1534735419878505. doi:10.1177/1534735419878505
131. Fan YF, Qin Y, Li DG, Kerr D. Retrospective Clinical Study of Advanced Pancreatic Cancer Treated With Chemotherapy and Abdominal Hyperthermia. *J Glob Oncol*. Sep 2018;4:1-4. doi:10.1200/jgo.2017.009985
132. Iyikesici MS. Long-Term Survival Outcomes of Metabolically Supported Chemotherapy with Gemcitabine-Based or FOLFIRINOX Regimen Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy in Metastatic Pancreatic Cancer. *Complement Med Res*. 2020;27(1):31-39. Langzeitüberlebens-Outcomes der metabolisch unterstützten Chemotherapie mit Gemcitabin oder FOLFIRINOX in Kombination mit ketogener Ernährung, Hyperthermie und hyperbarer Sauerstofftherapie beim metastasierenden Pankreaskarzinom. doi:10.1159/000502135
133. Petenyi FG, Garay T, Muhl D, et al. Modulated Electro-Hyperthermic (mEHT) Treatment in the Therapy of Inoperable Pancreatic Cancer Patients-A Single-Center Case-Control Study. *Diseases*. Nov 3 2021;9(4)doi:10.3390/diseases9040081
134. Fiorentini G, Sarti D, Ranieri G, et al. Modulated electro-hyperthermia in stage III and IV pancreatic cancer: Results of an observational study on 158 patients. *World J Clin Oncol*. Nov 24 2021;12(11):1064-1071. doi:10.5306/wjco.v12.i11.1064
135. van der Horst A, Versteijne E, Besselink MGH, et al. The clinical benefit of hyperthermia in pancreatic cancer: a systematic review. *Int J Hyperthermia*. Nov 2018;34(7):969-979. doi:10.1080/02656736.2017.1401126
136. DeWitt J, Yu M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK. Survival in patients with pancreatic cancer after the diagnosis of malignant ascites or liver metastases by EUS-FNA. *Gastrointest Endosc*. Feb 2010;71(2):260-5. doi:10.1016/j.gie.2009.08.025
137. Yonemori K, Okusaka T, Ueno H, Morizane C, Takesako Y, Ikeda M. FP therapy for controlling malignant ascites in advanced pancreatic cancer patients. *Hepatogastroenterology*. Dec 2007;54(80):2383-6.
138. Maluta S, Dall'Oglio S, Romano M, et al. Conformal radiotherapy plus local hyperthermia in patients affected by locally advanced high risk prostate cancer: preliminary results of a prospective phase II study. *Int J Hyperthermia*. Aug 2007;23(5):451-6. doi:10.1080/02656730701553260
139. Kalapurakal JA, Pierce M, Chen A, Sathiaseelan V. Efficacy of irradiation and external hyperthermia in locally advanced, hormone-refractory or radiation recurrent prostate cancer: a preliminary report. *Int J Radiat Oncol Biol Phys*. Nov 1 2003;57(3):654-64. doi:10.1016/s0360-3016(03)00625-4

140. Anscher MS, Samulski TV, Dodge R, Prosnitz LR, Dewhirst MW. Combined external beam irradiation and external regional hyperthermia for locally advanced adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. Mar 15 1997;37(5):1059-65. doi:10.1016/s0360-3016(97)00109-0
141. Nakahara S, Ohguri T, Kakinouchi S, et al. Intensity-Modulated Radiotherapy with Regional Hyperthermia for High-Risk Localized Prostate Carcinoma. *Cancers (Basel)*. Jan 13 2022;14(2)doi:10.3390/cancers14020400
142. Yahara K, Ohguri T, Yamaguchi S, et al. Definitive radiotherapy plus regional hyperthermia for high-risk and very high-risk prostate carcinoma: Thermal parameters correlated with biochemical relapse-free survival. *Int J Hyperthermia*. 2015;31(6):600-8. doi:10.3109/02656736.2015.1062214
143. Beck M, Ghadjar P, Mehrhof F, et al. Salvage-Radiation Therapy and Regional Hyperthermia for Biochemically Recurrent Prostate Cancer after Radical Prostatectomy (Results of the Planned Interim Analysis). *Cancers (Basel)*. Mar 6 2021;13(5)doi:10.3390/cancers13051133
144. 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. Clinical Trial, Phase III; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't. *The lancet Oncology*. 2010;11(6):561-570. doi:10.1016/S1470-2045(10)70071-1
145. Issels RD, Lindner LH, Verweij J, 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*. Apr 1 2018;4(4):483-492. doi:10.1001/jamaoncol.2017.4996
146. 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. Clinical Trial, Phase III; Journal Article; Multicenter Study; Randomized Controlled Trial; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't. *Annals of surgery*. 2014;260(5):749-54; discussion 754-6. doi:10.1097/SLA.0000000000000978
147. Aiba H, Yamada S, Mizutani J, et al. Clinical outcomes of radio-hyperthermo-chemotherapy for soft tissue sarcoma compared to a soft tissue sarcoma registry in Japan: a retrospective matched-pair cohort study. *Cancer Med*. Apr 2018;7(4):1560-1571. doi:10.1002/cam4.1366
148. Aiba H, Yamada S, Mizutani J, et al. Efficacy of radio-hyperthermo-chemotherapy as salvage therapy for recurrent or residual malignant soft tissue tumors. *Int J Hyperthermia*. 2018;35(1):658-666. doi:10.1080/02656736.2018.1518545
149. Bücklein V, Limmroth C, Kampmann E, et al. Ifosfamide, Carboplatin, and Etoposide (ICE) in Combination with Regional Hyperthermia as Salvage Therapy in Patients with Locally Advanced Nonmetastatic and Metastatic Soft-Tissue Sarcoma. *Sarcoma*. 2020;2020:6901678. doi:10.1155/2020/6901678
150. Eckert F, Gani C, Kluba T, et al. Effect of concurrent chemotherapy and hyperthermia on outcome of preoperative radiotherapy of high-risk soft tissue sarcomas. *Strahlenther Onkol*. Jun 2013;189(6):482-5. doi:10.1007/s00066-013-0312-7
151. Zschaeck S, Wust P, Melcher I, et al. Neoadjuvant chemotherapy plus radiation versus chemotherapy plus regional hyperthermia in high-grade soft tissue sarcomas: a retrospective comparison. *Int J Hyperthermia*. 2018;35(1):1-9. doi:10.1080/02656736.2018.1498137
152. Willner A, Fechner K, Agaimy A, et al. Neoadjuvant concurrent chemoradiotherapy with and without hyperthermia in retroperitoneal sarcomas: feasibility, efficacy, toxicity, and long-term outcome. *Strahlenther Onkol*. Dec 2021;197(12):1063-1071. doi:10.1007/s00066-021-01830-0
153. Baur A, Stäbler A, Wendtner CM, et al. MR-imaging changes of musculoskeletal soft-tissue sarcomas associated with neoadjuvant chemotherapy and hyperthermia. *Int J Hyperthermia*. Jul-Aug 2003;19(4):391-401. doi:10.1080/0265673021000058366
154. Fiegl M, Schlemmer M, Wendtner CM, Abdel-Rahman S, Fahn W, Issels RD. Ifosfamide, carboplatin and etoposide (ICE) as second-line regimen alone and in combination with regional hyperthermia is active in chemo-pre-treated advanced soft tissue sarcoma of adults. *Int J Hyperthermia*. Sep 2004;20(6):661-70. doi:10.1080/02656730410001714959

155. Issels RD, Abdel-Rahman S, Wendtner C, et al. Neoadjuvant chemotherapy combined with regional hyperthermia (RHT) for locally advanced primary or recurrent high-risk adult soft-tissue sarcomas (STS) of adults: long-term results of a phase II study. *Eur J Cancer*. Sep 2001;37(13):1599-608. doi:10.1016/s0959-8049(01)00183-6
156. 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(2):127-35. doi:10.3109/02656730903335995
157. Nakano H, Higaki S, Tateishi A. The efficacy of hyperthermia combined with radiation therapy for high-grade soft tissue sarcoma. *Anticancer Res*. Mar-Apr 1998;18(2b):1319-23.
158. Wendtner CM, Abdel-Rahman S, Krych M, et al. Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft tissue sarcomas. *J Clin Oncol*. Jul 15 2002;20(14):3156-64. doi:10.1200/jco.2002.07.146
159. Wendtner C, Abdel-Rahman S, Baumert J, et al. Treatment of primary, recurrent or inadequately resected high-risk soft-tissue sarcomas (STS) of adults: results of a phase II pilot study (RHT-95) of neoadjuvant chemotherapy combined with regional hyperthermia. *Eur J Cancer*. Sep 2001;37(13):1609-16. doi:10.1016/s0959-8049(01)00191-5
160. Spałek MJ, Borkowska AM, Telejko M, et al. The Feasibility Study of Hypofractionated Radiotherapy with Regional Hyperthermia in Soft Tissue Sarcomas. *Cancers (Basel)*. Mar 16 2021;13(6)doi:10.3390/cancers13061332
161. Issels RD, Mittermüller J, Gerl A, et al. Improvement of local control by regional hyperthermia combined with systemic chemotherapy (ifosfamide plus etoposide) in advanced sarcomas: updated report on 65 patients. *J Cancer Res Clin Oncol*. 1991;117 Suppl 4:S141-7. doi:10.1007/bf01613220
162. Hiraoka M, Nishimura Y, Nagata Y, et al. Clinical results of thermoradiotherapy for soft tissue tumours. *Int J Hyperthermia*. May-Jun 1995;11(3):365-77. doi:10.3109/02656739509022472
163. Fujiwara K, Kohno I, Sekiba K. Therapeutic effect of hyperthermia combined with chemotherapy on vulvar and vaginal carcinoma. *Acta Med Okayama*. Apr 1987;41(2):55-62. doi:10.18926/amo/31745
164. van der Zee J, González González 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*. Apr 1 2000;355(9210):1119-25. doi:10.1016/s0140-6736(00)02059-6
165. Uehara S, Omagari J, Hata K. Deep local and regional hyperthermia with annular phased array. *Strahlenther Onkol*. Oct 1989;165(10):715-6.
166. Emami B, Myerson RJ, Scott C, Gibbs F, Lee C, Perez CA. Phase I/II study, combination of radiotherapy and hyperthermia in patients with deep-seated malignant tumors: report of a pilot study by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys*. Jan 1991;20(1):73-9. doi:10.1016/0360-3016(91)90140-y
167. Feldmann HJ, Molls M, Heinemann HG, Romanowski R, Stuschke M, Sack H. Thermoradiotherapy in locally advanced deep seated tumours--thermal parameters and treatment results. *Radiother Oncol*. Jan 1993;26(1):38-44. doi:10.1016/0167-8140(93)90024-3
168. Sapozink MD, Gibbs FA, Jr., Egger MJ, Stewart JR. Abdominal regional hyperthermia with an annular phased array. *J Clin Oncol*. May 1986;4(5):775-83. doi:10.1200/jco.1986.4.5.775
169. Sapozink MD, Gibbs FA, Jr., Gates KS, Stewart JR. Regional hyperthermia in the treatment of clinically advanced, deep seated malignancy: results of a pilot study employing an annular array applicator. *Int J Radiat Oncol Biol Phys*. Jun 1984;10(6):775-86. doi:10.1016/0360-3016(84)90378-x
170. Sapozink MD, Gibbs FA, Jr., Egger MJ, Stewart JR. Regional hyperthermia for clinically advanced deep-seated pelvic malignancy. *Am J Clin Oncol*. Apr 1986;9(2):162-9. doi:10.1097/00000421-198604000-00012
171. Wielheesen DH, Smitt PA, Haveman J, Fatehi D, Van Rhoon GC, Van Der Zee J. Incidence of acute peripheral neurotoxicity after deep regional hyperthermia of the pelvis. *Int J Hyperthermia*. Jun 2008;24(4):367-75. doi:10.1080/02656730701881125
172. Uchibayashi T, Yamamoto H, Kunimi K, et al. Combined treatment of radiofrequency capacitive hyperthermia for urological malignancies. *Oncol Rep*. Sep 1994;1(5):937-40. doi:10.3892/or.1.5.937
173. Petrovich Z, Emami B, Kapp D, et al. Regional hyperthermia in patients with recurrent genitourinary cancer. *Am J Clin Oncol*. Dec 1991;14(6):472-7. doi:10.1097/00000421-199112000-00003

174. Pang CLK, Zhang X, Wang Z, et al. Local modulated electro-hyperthermia in combination with traditional Chinese medicine vs. intraperitoneal chemoinfusion for the treatment of peritoneal carcinomatosis with malignant ascites: A phase II randomized trial. *Mol Clin Oncol*. May 2017;6(5):723-732. doi:10.3892/mco.2017.1221
175. Cho C, Wust P, Hildebrandt B, et al. Regional hyperthermia of the abdomen in conjunction with chemotherapy for peritoneal carcinomatosis: evaluation of two annular-phased-array applicators. *Int J Hyperthermia*. Aug 2008;24(5):399-408. doi:10.1080/02656730801929915
176. Maeta M, Kaibara N, Nakashima K, et al. A case-matched control study of intrahepatoarterial chemotherapy in combination with or without regional hyperthermia for treatment of primary and metastatic hepatic tumours. *Int J Hyperthermia*. Jan-Feb 1994;10(1):51-8. doi:10.3109/02656739409009331
177. Grady ED, McLaren J, Auda SP, McGinley PH. Combination of internal radiation therapy and hyperthermia to treat liver cancer. *South Med J*. Sep 1983;76(9):1101-5. doi:10.1097/00007611-198309000-00008
178. Petrovich Z, Langholz B, Kapp DS, et al. Deep regional hyperthermia of the liver. A clinical study of 49 patients. *Am J Clin Oncol*. Oct 1989;12(5):378-83. doi:10.1097/00000421-198910000-00003
179. Amichetti M, Romano M, Cristoforetti L, Valdagni R. Hyperthermia and radiotherapy for inoperable squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site. *Int J Hyperthermia*. Jan-Feb 2000;16(1):85-93. doi:10.1080/026567300285448
180. Lloret M, García-Cabrera L, Zajac M, Lara PC. Regional deep hyperthermia in combination with whole brain radiotherapy (WBRT) in poor prognosis patients with brain metastases. *Clin Transl Oncol*. Jan 2021;23(1):190-194. doi:10.1007/s12094-020-02404-9
181. Dunlop PR, Hand JW, Dickinson RJ, Field SB. An assessment of local hyperthermia in clinical practice. *Int J Hyperthermia*. Jan-Mar 1986;2(1):39-50. doi:10.3109/02656738609019992
182. Lindholm CE, Kjellen E, Nilsson P, Hertzman S. Microwave-induced hyperthermia and radiotherapy in human superficial tumours: clinical results with a comparative study of combined treatment versus radiotherapy alone. *Int J Hyperthermia*. Sep-Oct 1987;3(5):393-411. doi:10.3109/02656738709140410
183. Scott RS, Johnson RJ, Story KV, Clay L. Local hyperthermia in combination with definitive radiotherapy: increased tumor clearance, reduced recurrence rate in extended follow-up. *Int J Radiat Oncol Biol Phys*. Nov 1984;10(11):2119-23. doi:10.1016/0360-3016(84)90211-6
184. Tsukiyama I, Yamashita K, Kajiura Y, et al. Results of a non-controlled trial of hyperthermia combined with radiation for superficial tumours. *Int J Hyperthermia*. Nov-Dec 1987;3(6):503-12. doi:10.3109/02656738709140423
185. Fujimura T, Yonemura Y, Fushida S, et al. Radiofrequency capacitive hyperthermia for superficial malignant-tumors. *Int J Oncol*. Jun 1993;2(6):1017-22. doi:10.3892/ijo.2.6.1017
186. Cruciani G, Molinari AL, Marangolo M, et al. Applicability of local hyperthermia as adjuvant to systemic chemotherapy. *Tumori*. Dec 31 1987;73(6):629-33.
187. Kihara T, Nakazawa H, Agishi T, Honda H, Ota K. Superiority of selective bolus infusion and simultaneous rapid removal of anticancer agents by charcoal hemoperfusion in cancer treatment. *ASAIO Trans*. Jul-Sep 1988;34(3):581-4.
188. Lloret M, García-Cabrera L, Hernandez A, Santana N, López-Molina L, Lara PC. Feasibility of a deep hyperthermia and radiotherapy programme for advanced tumors: first Spanish experience. *Clin Transl Oncol*. Dec 2019;21(12):1771-1775. doi:10.1007/s12094-019-02097-9
189. Petrovich Z, Langholz B, Gibbs FA, et al. Regional hyperthermia for advanced tumors: a clinical study of 353 patients. *Int J Radiat Oncol Biol Phys*. Mar 1989;16(3):601-7. doi:10.1016/0360-3016(89)90475-6
190. Baker HW, Snedecor PA, Goss JC, et al. Regional hyperthermia for cancer. *Am J Surg*. May 1982;143(5):586-90. doi:10.1016/0002-9610(82)90169-6
191. Feyerabend T, Steeves R, Wiedemann GJ, et al. Local hyperthermia, radiation, and chemotherapy in locally advanced malignancies. *Oncology*. May-Jun 1996;53(3):214-20. doi:10.1159/000227563
192. Bornstein BA, Herman TS, Hansen JL, et al. Pilot study of local hyperthermia, radiation therapy, etanidazole, and cisplatin for advanced superficial tumours. *Int J Hyperthermia*. Jul-Aug 1995;11(4):489-99. doi:10.3109/02656739509022484
193. Green DM, Burton GV, Cox EB, Hanson D, Moore J, Oleson JR. A phase I/II study of combined cisplatin and hyperthermia treatment for refractory malignancy. *Int J Hyperthermia*. Jan-Feb 1989;5(1):13-21. doi:10.3109/02656738909140429

194. Howard GC, Sathiaseelan V, King GA, Dixon AK, Anderson A, Bleehen NM. Regional hyperthermia for extensive pelvic tumours using an annular phased array applicator: a feasibility study. *Br J Radiol*. Dec 1986;59(708):1195-201. doi:10.1259/0007-1285-59-708-1195
195. Molls M, Feldmann HJ, Adler S, Sack H. Regional hyperthermia--a feasibility study. *Strahlenther Onkol*. Oct 1989;165(10):717-20.
196. Nakamura H, Hashimoto T, Fujita M, Matsui Y, Sawada S. Local hyperthermia combined with radiotherapy, chemotherapy, or arterial chemoembolization. *Radiat Med*. May-Jun 1990;8(3):103-6.
197. Pilepich MV, Myerson RJ, Emami BN, Perez CA, Straube W, von Gerichten D. Regional hyperthermia--assessment of tolerance to treatment. *Int J Radiat Oncol Biol Phys*. Feb 1988;14(2):347-52. doi:10.1016/0360-3016(88)90442-7
198. Van Es CA, Wyrdeman HK, de Leeuw AA, Mooibroek J, Lagendijk JJ, Battermann JJ. Regional hyperthermia of pelvic tumours using the Utrecht 'Coaxial TEM' system: a feasibility study. *Int J Hyperthermia*. Mar-Apr 1995;11(2):173-86. doi:10.3109/02656739509022455
199. U R, Noell KT, Woodward KT, Worde BT, Fishburn RI, Miller LS. Microwave-induced local hyperthermia in combination with radiotherapy of human malignant tumors. *Cancer*. Feb 15 1980;45(4):638-46. doi:10.1002/1097-0142(19800215)45:4<638::aid-cncr2820450404>3.0.co;2-f
200. Kakehi M, Ueda K, Mukojima T, et al. Multi-institutional clinical studies on hyperthermia combined with radiotherapy or chemotherapy in advanced cancer of deep-seated organs. *Int J Hyperthermia*. Jul-Aug 1990;6(4):719-40. doi:10.3109/02656739009140820
201. Perez CA, Scott C, Emami B, et al. Evaluation of 45 degrees C hyperthermia and irradiation. II. A phase I clinical trial in humans by the Radiation Therapy Oncology Group. *Am J Clin Oncol*. Dec 1993;16(6):477-81.
202. Seegenschmiedt MH, Brady LW, Rossmeissl G. External microwave hyperthermia combined with radiation therapy for extensive superficial chest wall recurrences. *Recent Results Cancer Res*. 1988;107:147-51. doi:10.1007/978-3-642-83260-4_21
203. Myerson RJ, Scott CB, Emami B, Sapozink MD, Samulski TV. A phase I/II study to evaluate radiation therapy and hyperthermia for deep-seated tumours: a report of RTOG 89-08. *Int J Hyperthermia*. Jul-Aug 1996;12(4):449-59. doi:10.3109/02656739609023523
204. Perez CA, Nussbaum G, Emami B, VonGerichten D. Clinical results of irradiation combined with local hyperthermia. *Cancer*. Nov 1 1983;52(9):1597-603. doi:10.1002/1097-0142(19831101)52:9<1597::aid-cncr2820520910>3.0.co;2-n
205. Fang H, Zhang Y, Wu Z, et al. Regional hyperthermia combined with chemotherapy in advanced gastric cancer. Journal: Article. *Open medicine (poland)*. 2019;14(1):85-90. doi:10.1515/med-2019-0012
206. Petrovics G, Szigeti G, Hamvas S, Mate A, Betlehem J, Hegyi G. Controlled pilot study for cancer patients suffering from chronic fatigue syndrome due to chemotherapy treated with BioBran (MGN-3-Arabinoxylane) and targeted radiofrequency heat therapy. Journal: Article. *European journal of integrative medicine*. 2016;8:29-35. doi:10.1016/j.eujim.2016.10.004
207. Ou J, Zhu X, Lu Y, et al. A phase I-II clinical trial to evaluate the safety, pharmacokinetics and efficacy of high dose intravenous ascorbic acid synergy with mEHT in Chinese patients with stage III-IV non-small cell lung cancer. 2017 %J Annals of oncology 2017;28:iii12-iii13.
208. Dobšíček Trefná H, Crezee J, Schmidt M, et al. Quality assurance guidelines for superficial hyperthermia clinical trials : II. Technical requirements for heating devices. *Strahlenther Onkol*. May 2017;193(5):351-366. Leitlinien zur Qualitätssicherung der lokalen Hyperthermie in klinischen Studien : II. Technische Anforderungen an Heizgeräte. doi:10.1007/s00066-017-1106-0
209. Lagendijk JJ, Van Rhoon GC, Hornsleth SN, et al. ESHO quality assurance guidelines for regional hyperthermia. *Int J Hyperthermia*. Mar-Apr 1998;14(2):125-33. doi:10.3109/02656739809018219
210. Izukura R, Imada H, Hashiguchi N, et al. Cardiac and respiratory effects of deep regional hyperthermia using an 8 MHz radiofrequency-capacitive device on patients with cancer. *Int J Hyperthermia*. Jun 2017;33(4):428-434. doi:10.1080/02656736.2017.1283064
211. FDA. Summary of Safety and Probable Benefit: BSD-2000 Hyperthermia System. 2011;
212. OncothermHightechMedicine. User's Manual EHY-2000plus. 2017;

213. Kok HP, Wust P, Stauffer PR, Bardati F, van Rhoon GC, Crezee J. Current state of the art of regional hyperthermia treatment planning: a review. *Radiat Oncol*. Sep 17 2015;10:196. doi:10.1186/s13014-015-0503-8
214. Datta NR, Bose AK, Kapoor HK, Gupta S. Head and neck cancers: results of thermoradiotherapy versus radiotherapy. *Int J Hyperthermia*. May-Jun 1990;6(3):479-86. doi:10.3109/02656739009140944
215. Baronzio GP, G. Ballerini, M. Szaz, A. . A Brief Overview of Hyperthermia in Cancer Treatment. *J Integr Oncol*. 2014;3(1)