Hyperthermia in Cancer Care: A Literature Review

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ABSTRACT

Introduction: Hyperthermia (HT) in cancer management refers to the external application of heat to raise intratumoural temperature to between 39°C and 45°C. Locoregional hyperthermia (LRHT) is the most used and studied type of HT in cancer care. A literature search was conducted to produce a monograph to help clinicians and patients make informed choices in considering the application of this therapy.

Methods: A search was performed in Medline and Cochrane library for LRHT and cancer in May 2020. Eligible studies were English-language clinical studies reporting on efficacy, quality of life (QoL), safety, or feasibility. Additional cursory literature scoping was performed to identify missing papers and background information. Papers were independently screened by two reviewers. Following development of a full monograph, a condensed version suitable for publication was created and is presented here.

Results: A total of 980 articles were identified and 166 met inclusion criteria. Most were single-arm or observational. However, among the 166, there were 7 systematic reviews (including 37 RCTs) and 18 additional RCTs identified. Several mechanisms of action have been proposed for HT in cancer care including physiological changes, direct cytotoxic effects, chemosensitization and radiosensitization, and immune modulation. Locoregional HT is used primarily as an adjunct to chemotherapy and radiotherapy due to its possible synergistic effects. Various studies demonstrated improved outcomes for patients treated with LRHT and chemo-and/or-radiotherapy. The best evidence for improved disease control and survival is seen 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 often focuses on pain. Hyperthermia with modern technology and treatment planning is generally well tolerated; the most common side effects are discomfort, mild pain, local erythema, skin burns, and, less commonly, subcutaneous burns. Trial heterogeneity and methodological concerns limit the strength of conclusions.

Conclusions: Locoregional HT is a promising adjunct treatment to chemotherapy and radiotherapy for a variety of cancer types. To determine in what situations this therapy could be best applied, more high-quality well-controlled studies are needed.

Key Words Locoregional Hyperthermia, Oncothermia, Oncology, Integrative Oncology, Naturopathic Oncology

INTRODUCTION

Hyperthermia (HT) for cancer involves heating cells and tissue to temperatures above the normally maintained range via exogenous means to selectively affect tumours. It is usually used in combination with conventional care.[1] Several types of HT exist: local (LHT), regional (RHT), interstitial and endocavitary, whole-body, hyperthermic isolated limb perfusion,[2] hyperthermic intraperitoneal chemotherapy (HIPEC), and hyperthermic intravesical chemotherapy (HIVEC).[3] Local and regional hyperthermia (locoregional hyperthermia; LRHT) is available in a few Canadian naturopathic practices. Local HT increases the temperature of superficial tumours using applicators or antennae over skin with a contact medium.[3] In RHT, deep tumours and body regions are heated by arrays of antennas; often arranged in a ring around the patient.[2] The applicators typically emit microwaves or radio waves to heat the tumour.[2] Locoregional HT aims to increase intratumoural temperature to 39–45°C, although 41–43°C is considered optimal.[4,5]

Despite many LRHT studies for cancer care, no comprehensive resource outlining clinical evidence exists. Therefore, a detailed

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and structured literature search was performed to evaluate the clinical efficacy of LRHT in cancer care, from which a comprehensive monograph was developed, and its adapted condensed review presented here.

METHODS

Medline and Cochrane Library were searched in May 2020 without date restrictions. Search terms included the neoplasm medical subject headings (MeSH) terms, and terms related to LRHT, including: local hyperthermia, locoregional hyperthermia, regional hyperthermia, modulated electrohyperthermia, external hyperthermia, part-body hyperthermia, and oncothermia. Scoping and reference reviews were performed to identify additional papers. Titles and abstracts were screened in duplicate, followed by single-review of full-text publications (Figure 1).

Inclusion criteria included English-language studies of human populations with cancer receiving external LRHT. Studies could investigate outcomes related to clinical effectiveness (e.g., survival, recurrence, response), quality of life (QoL), safety, adverse events (AEs) and feasibility. Eligible study designs included systematic reviews and meta-analyses, clinical trials, and observational studies. Exclusion criteria included preclinical trials, narrative reviews, case studies, other types of HT, and/or technical studies on HT instrumentation. Studies accounted for in systematic reviews or meta-analyses were excluded to not be described twice.

This literature review is a condensed version derived from the full monograph for LRHT and cancer care. The cancers with the most available evidence are the focus of this condensed literature review. Studies of patients with mixed cancer types were omitted due to space limitations and heterogeneous participant samples, designs, and quality. Complete details can be found in the full monograph by contacting the corresponding author.

RESULTS

A total of 1,000 articles were identified. Scoping and reference review identified an additional 25 papers. After deduplication, 980 articles were screened, and 166 were included in the monograph (Figure 1). This condensed literature review, which does not discuss mixed cancer types, includes 126 papers.

Efficacy

Cancer types with the most rigorous research are described henceforth in detail. Systematic reviews and meta-analyses are described in Table 1, and randomized controlled trials (RCTs) in Table 2. Full discussion of all data identified in the original literature search can be found in the healthcare provider monograph; please contact the corresponding author for more information and access details.

Breast Cancer

One meta-analysis (31 articles reporting on 34 studies)[11] and two single-arm trials[31,32] were identified. The meta-analysis included five RCTs, three non-randomized controlled trials, and 26 single-arm trials, all of which investigated LRHT combined with radiation (RT) for locally recurrent breast cancer.[11] Based on

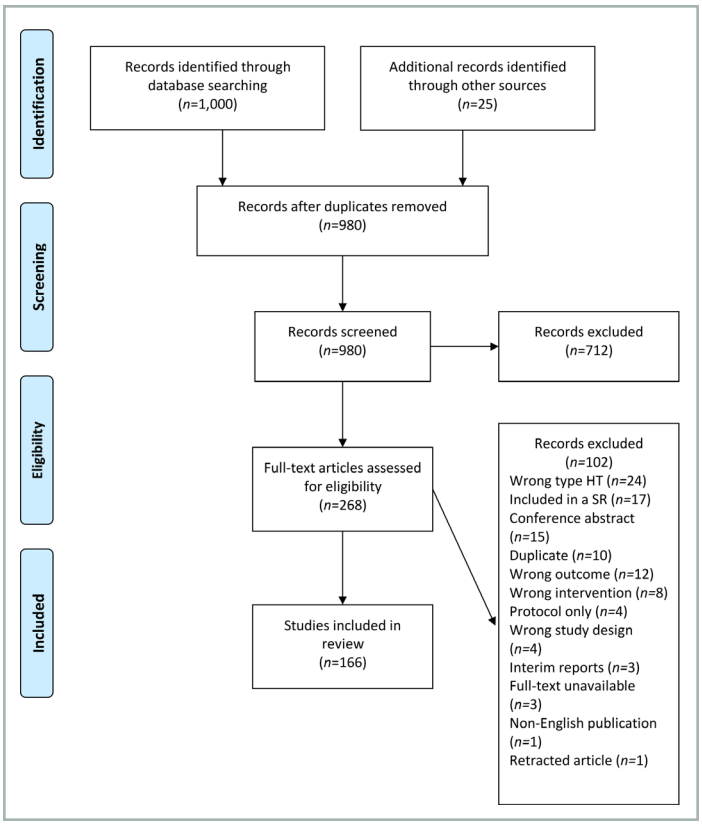

FIGURE 1 Prisma flow diagram. HT = hyperthermia; SR = systematic review.

controlled trials (both randomized and non-randomized) from the meta-analysis, the complete response (CR) rate was 60.2% in the combination group and 38.1% in the control group (odds ratio [OR]: 2.64; 95% confidence interval [CI]: 1.66–4.18, $p < 0.0001$). Based on single-arm trials, the CR rate was 63.4%. Mean acute and late grade III/IV toxicities were higher in the hyperthermia group compared with the control (14.4% vs 5.2%). As publication dates spanned 34 years, no uniform toxicity scoring criteria or review could be presented.

Two single-arm studies not included in the meta-analysis were identified.[31,32] The first reported jointly on two phase I studies including 29 patients with chest-wall recurrences, all of whom had received prior standard treatments.[31] Locoregional HT delivered within 30 to 60 minutes of doxorubicin resulted in a response rate of 48.3%, with 17.2% having CR. All adverse events (AEs) were reported as chemotherapy-related. The second single-arm trial ($n = 7$) applied chemotherapy and LRHT simultaneously for patients with recurrent, inoperable breast cancer who had received prior conventional care.[32] All participants experienced an objective response (OBJR), with four CR and three partial responses (PR). Median time to recurrence was six months.

Cervical Cancer

Two systematic reviews with meta-analysis[7,8] (reporting on seven RCTs), five publications on three RCTs,[19,20,28,29,33] and six single-arm trials were included.[34-39]

The latest systematic review, which performed two separate analyses (conventional and network meta-analysis) of LRHT for

TABLE 1 Systematic reviews and meta-analyses of locoregional hyperthermia (LRHT) for cancer

Reference	Study Design	# of Trials and Participants	Population	Intervention	Control	Results
Hu et al., 2017[6]	Systematic review and meta-analysis	19 RCTs (n=1,519)	Esophageal cancer – mixed staging	Hyperthermia chemo-radiotherapy (HCRT)	Chemo-radiotherapy (CRT) or radiotherapy (RT)	**HCRT vs CRT** *1-, 3-, 5-, 7-yr 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-yr survival was not statistically 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-yr 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 towards higher rates of GI reactions, leukocytopenia, and radiation oesophagitis and a trend towards lower rates of radiation pneumonitis.
Datta et al., 2016[7]	Systematic review and meta-analysis	Conventional meta-analysis: 6 RCTs (n=427) Network meta-analysis: 8 trials (7 RCTs, 1 meta-analysis, n=1,160)	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) and 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[8]	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 *OS:* HR 0.67, 95% CI 0.45–0.99, p = 0.05 *Toxicities:* no significant difference in acute or late toxicity between arms

TABLE 1 (cont'd)

Reference	Study Design	# of Trials and Participants	Population	Intervention	Control	Results
Van der Horst et al., 2018[9]	Systematic review	14 studies (n= 395); 8 studies used LRHT (n=189) None were RCTs, all were observational (8 retrospective, 6/14 included a control 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%)	*RR (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. *Note:* Full meta-analysis was not done due to quality of studies. These results were not exclusive for LRHT, but combined multiple types of HT
Datta et al., 2016[10]	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 with RT alone.
Datta et al., 2015[11]	Systematic review and meta-analysis	31 papers (reporting on 34 studies); 6 single-arm studies, 5 RCTs, 3 non-randomized controlled (n=1,792)	Breast cancer - Local/regional recurrence	Hyperthermia + radiotherapy (HTRT) HT most often applied 2x/week following radiation, mean temperature 42.5 °C	Radiotherapy (RT)	***Controlled clinical trials*** *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[12]	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 range 38–45.5°C	Mixed conventional care alone	RFS at 24 months was reported in 2 single-arm trials: 78% and 33%, respectively. *CR 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)

RCT = randomized controlled trial; HCRT = hyperthermia chemotherapy radiotherapy; CRT = chemoradiotherapy; RT = radiation; OR = odds ration; CI = confidence interval; GI = gastrointestinal; HTRT = hyperthermia radiotherapy; NNT = number needed to treat; SUCRA = surface under the cumulative ranking curve; OS = overall survival; RR = response rate; HT = hyperthermia; AE = adverse event.

patients with locally advanced cervical cancer, was published in 2016.[7] In the conventional meta-analysis conducted (6 RCTs, n = 427), HT with radiotherapy (HTRT) was found to outperform RT for CR (OR 2.67, 95% CI 1.57–4.54, p < 0.001) and long-term locoregional control (OR 2.61, 95% CI: 1.55–4.39, p < 0.001). Overall survival (OS) was superior in the HTRT group compared with RT (OR 1.94, 95% CI 1.10–3.40, p = 0.021). However, risk difference was not significant (8.4% difference, p = 0.299). In the network meta-analysis conducted (7 RCTs, n = 1,160), HT combined with chemotherapy and radiation (HTCTRT) was superior to chemotherapy combined with radiation (CRT) (OR 2.91, 95% CI 1.97–4.31), and RT (OR 4.52, 95% CI 1.93–11.78) for CR. The OS in the HTCTRT group was superior to chemoradiotherapy (CRT) (OR 2.65, 95% CI 1.51–4.87) and RT (OR 5.57, 95% CI 1.22–23.42). A 2010 Cochrane review found similar results.[8]

Three controlled trials yielded five publications since the last systematic review.[19,20,28,29,33] One multicentre RCT (n = 101) that included treatment-naive patients with locally advanced cervical cancer reported that the addition of LRHT to CRT did not improve overall five-year survival (adjusted hazard ratio [HR]: 0.485, 95% CI: 0.217–1.082, p = 0.077), disease-free survival (DFS) (adjusted HR: 0.517, 95% CI: 0.251–1.065, p = 0.073), local relapse-free survival (LRFS) (p > 0.05) or CR (p > 0.05) compared with CRT alone.[20]

TABLE 2 Randomized controlled trials of locoregional hyperthermia (LRHT) for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Issels et al., 2010[13]	Multicentre phase III, open label RCT, (EORTC 62961-ESHO 95 Trial)	*N*=341 (Tx 169, control 172) **Soft-tissue sarcoma (STS)** – adults with localized STS (tumour 5 cm 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, tumour 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) ***Secondary outcomes*** *DFS:* Relative hazard 0.70 (95% CI 0.54–0.92, p=0.011) for Tx compared with 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 control arm (77.6% vs 63%, p=0.005)
Angele et al., 2014[14]	Subgroup analysis of (EORTC 62961 –ESHO 95 Trial) Phase III, multicentre, open-label RCT	*N*=149 (subgroup of the total 341-person population) **Soft-tissue sarcoma (STS)** – adults with abdominal or retroperitoneal high-risk sarcoma, who had macroscopic complete resection (R0, R1).	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)	Local PFS, DFS, OS after 5-year follow-up	*Local PFS:* 56% in Tx arm vs 34% in control arm (p=0.044) *DFS:* 34% in Tx arm vs 27% in control arm (p=0.04) *OS:* no difference between groups (57% vs 55% in Tx vs control)
Issels et al., 2018[15]	Long-term outcomes of the EORTC 62961 – ESHO 95 Trial Phase III, multicentre, open-label RCT	*N*=341 (Tx 169, control 172) **Soft-tissue sarcoma (STS)** – adults with localized STS (tumour 5 cm 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)

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Fang et al., 2019[16]	RCT	*N*=118 (55 in Tx, 63 in control) **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	ORR (CR + PR) Disease control rate (DCR) (CR, PR, SD) OS Safety	*Disease control rate:* 70.9% and 46.0% for HTCT and control groups respectively (p=0.006) *mOS:* 23.5 months for HTCT group and 14 months for control (p=0.01) *3-yr survival rate:* RHCT 11.4%, control 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[17]	RCT	*N*=18 (9 in Tx, 9 in control) **Metastatic melanoma** – refractory to other treatments, with an accessible tumour mass	Local HT + intratumoural dendritic cell (DC) injections HT administered for 1 hour prior to DC injection (42–43°C), 3x in week 1 of a 28-day cycle, up to 2 cycles administered	Intratumoural injection of dendritic cells (DC) alone	ORR (CR + PR) and DCR (CR + PR + SD) Time to progression (TTP) Survival Toxicity Melanoma-specific antitumour immunity	***DC Response*** 77.8% in Tx arm, 44.4% in control arm, p<0.05. *Tx arm:* 1 CR, 3 PR, and 3 SD. *Control arm:* 1 PR and 3 SD. *TTP:* 5 months and 2 months Tx and control 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 control 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. *Antitumour immunity:* Cell assays demonstrated some possible anti-tumour 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[18]	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 control arm (p<0.05) *2-yr local tumour 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, tumour size. *Safety:* Addition of heat did not increase acute or late effects of radiation.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Minnaar et al., 2019[19]	Phase III RCT, preliminary results	*N*=202 (101 in mEHT, 101 in control) **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 with 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[20]	Multicentre, open-label, RCT	*N*=101 (50 control, 51 Tx) **Cervical cancer** – stage IIA–IVA, treatment naïve	HT + chemoradiotherapy Whole-pelvis hyperthermia (43°C) delivered once weekly concurrently with cisplatin + radiotherapy for 60 minutes, delivered for the duration of 3–5 chemoradiotherapy cycles	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). *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[21]	Multicentre, open-label, RCT	*N*=80 (40 control., 40 Tx) **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-yr local PFS:* Significantly higher in the HT group (67.5%) compared with control (29.0%) (*p*=0.036). *1-yr OS:* Not significantly different between groups (*p*=0.868).
Shen et al., 2011[22]	Phase II RCT	*N*=80 (40 control., 40 Tx) **NSCLC:** advanced, stage IIIB–IV	HT + chemotherapy One hour after chemotherapy (cisplatin + gemcitabine), patients received HT (300–1,100 W), for 60 minutes, 2x/week. Target temperature 39–42.5 °C.	Gemcitabine + cisplatin, without HT	Tumour response, toxicity/AE, QoL, Clinical Benefit Response (CBR)	*Response rate:* No significant difference between groups *Global QoL:* HT group significantly improved compared with control; however, no differences among specific components
Shchepotin et al., 1994[23]	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, every day for 4 consecutive days prior to surgery (pre-operative phase). Tumour 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 with radiation alone. Compared with surgery alone, radiation + hyperthermia significantly improved 5-yr survival *p*<0.05.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Petrovics et al., 2016[24]	RCT Pilot Study	*N*=50 (25 Tx, 25 control.) Mix of cancer types – all patients suffering from chronic fatigue syndrome	HT + Biobran (MGN-3-arabinoxylane) HT delivered 1x/week for 15 weeks. Unclear whether they also received standard care	Standard care (chemotherapy and radiation)	QoL, fatigue	*Whole-body pH*: Compared with baseline, HT group is reported to have significantly normalized whole body pH ($p<0.01$) *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[25]	Phase II RCT	*N*=260 (Tx: 130, control: 130) **Mixed peritoneal cancers:** stage III–IV with the presence of malignant ascites	HT + TCM herbal medicine HT was 60 minutes, every second 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 with control (63.85%) $p=0.005$. A non-significant benefit was noted for complete response in the Tx group compared with control. *KPS score:* significantly improved in Tx group compared with control $p<0.05$. *Adverse events:* occurred significantly more in the control group (16 cases) compared with Tx group (3 cases) $p<0.05$
Ou et al., 2017[26]	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	*QoL:* the only measure that significantly improved compared with baseline was physical functioning. No significant between-group QoL differences/changes were found.
Ou et al., 2020[27]	Phase II RCT	*N*=97 (Tx: 49, control: 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, DCR, survival, AE, QoL	*Median OS:*9.4 months in Tx group compared with 5.6 months in control (HR: 0.33, 95% CI: 0.16–0.41, $p<0.0001$. *Median PFS:* 3 months in Tx group compared with 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 with 16.7% in control ($p=0.0073$). *QoL:* physical, emotional, and global improvements were significantly better in Tx group. Significant improvements were noted for symptoms such as fatigue, pain, nausea, SOB and appetite loss in the Tx group compared with control. *Biomarker changes:* no significant changes observed
Minnaar et al., 2020[28]	Phase III RCT	*N*=206 (control: 101, Tx: 105) **Cervical cancer:** stage IIB–III, HIV positive (CD4+ count > 200)	HT + radiation + cisplatin Immediately before radiation, patient received HT for 55 minutes, 2x/week. Patients also received cisplatin.	Radiation + cisplatin alone	Toxicity, QoL	*QoL:* At the 6-week mark, cognitive function was significantly higher in the HT group compared with control. At the 3-month mark, fatigue and pain were significantly reduced in the HT group. At the 3-month mark, compared with baseline, social functioning significantly improved.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Minnaar, et al., 2020[29]	Phase III RCT *Sub-analysis of Minnaar et al., 2020[28]	*N*=108 (Tx: 54, control: 54) **Cervical Cancer:** Tx group: 25 HIV+, 29 HIV–; control 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 with control (5.6%) (p=0.013).
Van der Zee et al., 2000[30]	Multicentre RCT	*N*=358 (control: 176, Tx: 182) **Mixed Cancer:** bladder cancer (T2–T4, N0, M0), 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 with control (58 vs 37%, respectively, p=0.003). Patients with cervical cancer and bladder cancer had significantly better CR rates 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 tumour 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-yr follow up, only patients with cervical cancer had a significantly better OS (51% vs 27%, p=0.009).

RCT = randomized controlled trial; EORTC = European Organisation for Research and Treatment of Cancer; ESHO = European Society of Hyperthermic Oncology; NNT = number needed to treat; CI = confidence intervals; STS = soft-tissue sarcoma; Tx = treatment; FNCLCC = French Federation of Cancer Centers Sarcoma Group; HT = hyperthermia; PFS = progression-free survival; DFS = disease-free survival; LRFS = local recurrence-free survival; OS = overall survival; mOS = median overall survival; AE = adverse event; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RHCT = regional hyperthermia and chemotherapy; TTP = time to progression; LHT = local hyperthermia; DC = dendritic cell; DCR = disease control rate; LN = lymph node; CRT = chemoradiotherapy; HTRT = hyperthermia radiotherapy; HCRT = hyperthermia chemoradiotherapy; mEHT = modulated electrohyperthermia; FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma; LRHT = locoregional hyperthermia; RT = radiotherapy; QoL = quality of life; HR = hazard ratio; OR = odds ratio; NSCLC = Non-small cell lung cancer; TCM = traditional Chinese medicine; IVC = intravenous vitamin C; KPS = Karnofsky performance status; SOB = shortness of breath.

Three papers published data from an ongoing phase III RCT investigating modulated electro-hyperthermia (mEHT) with CRT, compared with CRT alone, for patients with stage IIB–IIIB cervical cancer.[19,28,29] Patients from a low-resource African setting were treated with mEHT twice weekly before RT in addition to cisplatin-chemotherapy. The first publication reported early results.[19] At six months, the local disease control and local DFS were superior in the mEHT group than in the control (45.5% vs 24.1%, p = 0.003; 38.6% vs 19.8%, p = 0.003, respectively). The second publication found no significant difference in treatment toxicity between study arms, and AEs attributed to mEHT were minor.[29] There was some evidence of QoL improvement, specifically for cognitive function, post-treatment fatigue, and social and emotional functioning in the HT arm. The third publication evaluated the abscopal effect in a subgroup of patients with involved lymph nodes outside of the treatment field.[28] Participants in the LRHT arm experienced significantly higher complete metabolic response (abscopal effect marker) than the control (24.1% vs 5.6%, p = 0.013).

Lastly, a controlled clinical trial in patients with recurrent, previously irradiated cervical cancer administered platinum-based chemotherapy with (n = 18) or without (n = 20) mEHT.[33] Objective response rates were superior in the mEHT group than in the control (p = 0.046). However, there was no significant OS difference.

Six phase I and II studies were identified.[34-39] Four phase I/II studies evaluated LRHT administered with cisplatin in patients with pelvic recurrences.[34,36,38,39] The first study found that LRHT alongside six-weekly cisplatin treatments in 19 patients produced

an overall response rate of 53% with no dose-limiting toxicities.[34] An additional 28 people were enrolled and the full dataset of 47 people was published separately.[38] The OBJR rate from that publication was 58%, with a median OS of eight months. In patients with pain, 74% achieved palliation. A phase II study administered LRHT simultaneously with cisplatin in 23 patients.[36] The response rate was 52%, median duration of response 9.5 months, mean OS 8 months, and one-year survival 42%. Another phase I/II study in patients with treatment-naive stage IIB–IVA cervical cancer published early[39] and late results.[37] Sixty-eight people were treated with RT, weekly cisplatin, and four weekly-whole pelvis LRHT treatments. Complete response was observed in 90% of patients. Two-year DFS and OS were 71.6% and 78.5%, respectively, and five-year DFS and OS were 57.5% and 66.1%, respectively. Lastly, a phase II study administered LRHT to 18 patients with advanced cervical cancer receiving 28-fractions of RT.[35] Thirteen patients had a CR, four patients a partial response, and there was a local control rate of 48% at two years.

Esophageal Cancer

One meta-analysis (19 RCTs),[6] two single-arm trials,[40,41] and one observational trial[42] were identified. The meta-analysis (n = 1,519) published in 2017 compared HTCTRT with CRT and RT.[6] Compared with CRT, HTCTRT significantly improved one-year survival (OR 1.79, 95% CI 1.12–2.84, p = 0.01), three-, five-, and seven-year survival, but not two-year survival. In terms of response rate, HTCTRT significantly improved the rate compared with CRT alone (OR 2.00, 95% CI 1.49–2.69, $p < 0.00001$) but did not significantly alter recurrence or distant metastasis rates. HTCTRT decreased several adverse effects of CRT, including gastrointestinal reactions, leukocytopenia, and esophagitis. When comparing HTCTRT with RT, HTCTRT significantly improved one-year survival (OR 3.2, 95% CI 2.07–4.95, $p < 0.00001$) and survival at two, three, and five years. Quality of the individual RCTs was generally low.

Two single-arm studies[40,41] and one observational study[42] were also reviewed. The phase I/II study evaluated feasibility and toxicity of combined chemotherapy and LRHT for patients with esophageal cancer.[41] Locoregional HT administered on day 1 of neoadjuvant chemotherapy was feasible with acceptable toxicity. Another phase II study enrolled 28 people with resectable esophageal cancer and applied neoadjuvant CRT with LRHT.[40] The response rate was 74%, with 19% having a CR. After a median follow-up of 37 months, locoregional disease control was 100%, one-year, two-year, and three-year survival were 79%, 57%, and 54%, respectively. Lastly, one retrospective observational study evaluated combined radiotherapy and LRHT with or without cisplatin to patients with supraclavicular lymph node metastasis.[42] The three-year progression-free survival (PFS) and OS were 34.9% and 42.5%, respectively.

Gastric Cancer

Two RCTs,[16,23] one single-arm study,[43] and two observational studies[44,45] were identified.

A phase II RCT (n = 118) enrolled patients with advanced gastric cancer who received chemotherapy with or without LRHT twice per week.[16] For the HCT group compared with the chemotherapy group, the disease control rate (CR/PR/Stable Disease) was 70.9% vs 46.0% (p = 0.006), mean OS was 23.5 months vs 14 months (p = 0.01), and the three-year survival rate was 11.4% vs 0% (p = 0.018). There were no group differences in grade III/IV AEs.

Another large (n = 293) three-armed RCT randomized patients with newly diagnosed non-metastatic gastric cancer to surgery alone, preoperative RT, or preoperative HTRT.[23] Compared with surgery alone, HTRT significantly improved three-year survival (57.6% ± 6.3 vs 35.5% ± 4.9, $p < 0.05$) and five-year survival (51.4% ± 6.6 vs 30.1 % ± 4.7, $p < 0.05$). Radiotherapy alone did not significantly improve survival compared with surgery alone. There was no significant difference between survival for the RT group and the HTRT group, indicating no advantage of adding HT.[23]

The small single-arm study evaluated LRHT in 25 patients with unresectable, recurrent gastric cancer.[43] Amongst nine patients who had peritoneal carcinomatosis treated with LRHT, the survival outcomes were superior to a historical comparator (12.8±8.6 months vs 6.4±5.0 months, $p < 0.01$), but poor design and reporting limit generalizability.

One of the observational studies (retrospective) administered regional abdominal LRHT during intraperitoneal cisplatin for patients with stage IIA–IIIC surgically resected gastric cancer who were also receiving IV 5FU and leucovorin.[44] After 58 months, 68.2% recurred and 45.5% had died. Lastly, the other retrospective study evaluated a multimodal intervention of chemotherapy, ketogenic diet, insulin induced hypoglycemia, hyperbaric oxygen therapy (HBOT), and mEHS in patients (n = 25) with stage III/IV gastric cancer.[45] The treatment was administered in a three-week cycle of chemotherapy with HT and HBOT given sequentially for 60 minutes each on the day of, or day after, chemotherapy. The CR rate was 88%, mean OS 39.5 months (95% CI 28.1–51.0), and mean PFS was 36.5 months (95% CI: 25.7–47.2). There were no AEs attributed to the ketogenic diet, mEHT, or HBOT.

Head and Neck Squamous Cell Carcinoma

One systematic review and meta-analysis[10] (six controlled trials), one non-randomized controlled trial,[46] five single-arm clinical trials,[47-51] and three observational studies[52-54] were identified. The 2016 systematic review and meta-analysis of LRHT with RT for primarily locally-advanced head and neck cancer (HNC) reviewed six studies (five RCTs).[10] One study used intracavitary HT, which is outside the scope of this review. However, it does not appear that the findings would significantly skew the results. The CR rate of RT alone was 39.6% compared with 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 indicated no publication bias. However, there were a small number of studies included. Rates of grade III/IV toxicities were similar between groups.

Two single-arm studies evaluated LRHT with RT for HNC. One of the phase I/II studies delivered LRHT and RT to 27 patients with cervical lymph node metastasis.[47] The response rate was 92%, and the five-year nodal control and survival were 64.5% ± 19%, and 24% ± 10%, respectively. The other phase I/II single-arm

trial[48] included 13 participants with parotid cancer and administered HTRT. Complete response was observed in 16/20 lesions and PR in the remaining four.

Three single-arm trials and one observational study evaluated combined LRHT and CRT.[49,50,52,55] All three trials administered radiation five times per week with weekly chemotherapy and twice weekly LRHT. In one study, 53 patients with HNC with N2 or N3 metastatic cervical lymph nodes were treated.[49] The local CR rate was 82% and the PR rate 9%; the nodal CR rate was 85% and the PR rate 9%. At two years, the OS and DFS were 51% ± 9% and 54% ± 8%. Treatment toxicity was deemed acceptable. In the second study, 20 patients with previously treated recurrent metastatic cervical LNs were included.[50] Symptom palliation (pain, bleeding, difficulty breathing, difficulty swallowing, difficulty speaking) occurred in 19/20 patients. Response rates included 8/20 with a CR and 11/21 with a PR. The one-year OS was 39% ± 11%, with three patients alive at three years. Adverse events were generally grade 1 to 2 hematological and skin toxicity. A retrospective analysis of 40 patients with advanced HNC given seven weeks of radiation and once weekly LRHT and chemotherapy reported CR and PR rates of 76.23% and 23.68%, respectively, and one-year and two-year OS of 75.69% and 63.08%, respectively.[52]

Three small studies evaluated LRHT with chemotherapy.[46,51,54] A non-randomized controlled trial administered chemotherapy alone or with LRHT for patients with nodal-metastatic HNC.[46] The overall tumour response rate was 36% in the control group, compared with 100% in the intervention group (no statistics presented). In another study (pilot), eight patients with advanced or recurrent disease were treated with carboplatin plus LRHT once every four weeks for 1 to 3 rounds.[51] There was one CR and two PRs. Six patients died within 4 to 13 months, with two long-term survivors. The last study (n = 31) included patients with local squamous cell carcinoma (SCC) of the lip treated with twice weekly IV bleomycin and methotrexate, followed by HT for 4.5 to 7.5 weeks, reporting a CR and PR rate of 93.55% and 6.45%, respectively.[54] Among those experiencing CR, during a five-year follow-up there was one local recurrence and one death. Authors noted good cosmetic results.

Lastly, a small retrospective analysis evaluated LRHT with radiation and cetuximab.[53] Six patients with locally advanced SCC were treated with radiation for six to seven weeks, with once weekly cetuximab and LRHT. All patients experienced a CR; side effects included mucositis and acneiform rash.

High-Risk Soft-Tissue Sarcoma (STS)

One RCT (yielding three publications),[13-15] five observational studies[56-60], and seven single-arm trials[61-67] were identified. Additionally, one single-arm trial[68] included deep seated sarcomas, and one observational study mixed soft tissue tumours.[69]

The RCT (multicentre), which included patients with localized, high-risk soft-tissue sarcoma (STS), found the addition of regional HT enhanced the effect of chemotherapy.[13] Participants (n = 341) were randomized to receive four three-week cycles of chemotherapy with or without HT (days 1 and 4). Following surgery and/or radiation, patients received another four cycles of their allocated treatment. The first publication from this trial reported that after a 34-month median follow-up, the HT arm had superior PFS (HR 0.58, 95% CI 0.41–0.83, p = 0.003) and an absolute difference in PFS of 15% at two years (CI 6%–26%). Disease-free survival (HR 0.70, 95% CI 0.54–0.92), treatment response rate (28.8% vs 12.7%, p = 0.002), and OS (HR 0.66, 95% CI 0.45–0.98) were also improved in the regional HT arm compared with the control arm. Grade III/IV leukopenia was greater in the regional HT arm (77.6%, vs 63%, p = 0.005). Hyperthermia-related AEs included pain, bolus pressure, and skin burn. In 2018, a long-term analysis of the same study was published.[15] After a median follow-up of 11.3 years, the RHT arm experienced a significantly improved local PFS (HR: 0.65; CI: 0.49–0.86, p = 0.002). Combination treatment resulted in significantly prolonged survival rates compared with the control (HR: 0.73, 95% CI: 0.54–0.98, p = 0.04). This trial produced one additional publication with a sub-group analysis of patients with abdominal or retroperitoneal high-risk STS.[14] The regional HT plus chemotherapy arm had improved five-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 controlled observational studies were identified; one used a Bone and Soft Tissue Tumor (BSTT) registry for comparison purposes,[56] and the others compared results with RT or CRT alone.[59,60] The BSTT registry comparison study reported that patients who received LRHT during chemotherapy (post-radiotherapy) did not experience a significant five-year OS benefit (78.3% vs 81.2%, p = 0.33). In the LRHT arm, the local-control rate at five years was significantly better (97.7% vs 85.1%, p = 0.017), and negative surgical margins were significantly higher (p < 0.0001). The other two controlled studies[59,60] both reported no significant benefit from LRHT, including local control (p = 0.39), DFS (p = 0.69), and response (p = 0.67). One of them[59] reported that cancer-specific mortality was significantly better compared with the control (p = 0.03), while the other[60] showed no significant benefit for two-year OS, local-control survival, or distant metastasis-free survival.

Two uncontrolled observational studies were identified. One included 64 participants with recurrent or residual STS who received LRHT with CRT.[57] Five-year survival was 86.4% (± 7.3%) and the local control rate was 86.7% (± 7.1%). The other study included 110 participants with locally advanced high-risk STS receiving combined chemotherapy and LRHT.[58] Disease control occurred in 59% of non-metastatic cases and 47% in those with metastases, with a median OS of 26 and 12 months, respectively.

Seven single-arm trials evaluated LRHT in combination with various treatments. Two of them applied LRHT with chemotherapy alone, with one[61] delivering LRHT in patients with high-grade STS on days 1 and 4 of neoadjuvant chemotherapy. After four cycles, mean tumour volume reduction was 49% (5% to 91%, SD: 27%). The other trial included patients with doxorubicin/ifosfamide-refractory STS receiving chemotherapy, seven of whom received LRHT.[62] Two of the seven patients experienced a PR.

Five single-arm trials explored LRHT specifically added to standard peri-operative care.[63-67] In one, 13 patients received LRHT and radiation, with five participants receiving pre-operative chemotherapy and seven post-operative chemotherapy.[65] Limb

salvation was possible for 12 of 13 patients; there was no local recurrence; the five-year survival was 40.4%, and DFS was 30.1%. Mean tumour volume reduction was 68.2%, with no participants experiencing CR, seven PR, three no change, and three progressing. Another study (n = 58) explored the use of combined LRHT with chemotherapy in both the neoadjuvant and post-treatment phase.[66] The overall OBJR rate (based on 40 evaluable patients) was 13%. Radiological response was 33%, and of the 30 who underwent treatment, six experienced pathological CR (23%). Median time to local relapse or progression was 21 months, with a median five-year OS of 31 months. One publication combined data from two phase II trials, exploring the use of neoadjuvant CRT and LRHT, surgery, and adjuvant CRT (without LRHT).[64] The OBJR rate (evaluable in 39 participants) was 21% with a median OS of 105 months. Five-year OS was 57%, with a five-year local recurrence-free survival of 48%. A similar single-arm phase II trial applied LRHT pre-operatively alongside chemotherapy, followed by post-operative radiation when indicated. Responders received additional chemotherapy and LRHT after surgery. The OBJR rate was 17%, median survival was 52 months, and five-year OS was 49%. The combination of pre-operative chemotherapy and LRHT, with radiation applied post-operatively, was further explored in another single-arm trial (n = 59).[63] The OBJR rate was 17%, with one CR and eight PR. Out of the total group, 49 were eligible for surgery. The overall five-year rate of local relapse-free survival was 40% and the median survival was 52 months, with a five-year OS of 49%. One final study delivered LRHT in combination with neoadjuvant chemotherapy for patients with poorly resected, non-metastatic, STS.[67] The overall OBJR rate was 16%, of which all were partial. Median time to local relapse or progression was 21 months, median OS was 33 months, and the four-year OS rate was 40%.

General Soft Tissue Tumours

Two studies included patients with malignancies other than STS. One single-arm trial included a mix of different deep-seated, advanced sarcomas.[68] In addition to standard supportive care, participants received LRHT with chemotherapy. Based on 61 evaluable participants, overall OBJR was 34%, and 13 patients who were initially deemed to have unresectable disease were eligible for surgery. One observational study included patients with unresectable and/or recurrent mixed soft-tissue tumours, applying a combination of LRHT and radiation.[69] This produced a CR in 42% of tumours treated, with a five-year survival of 32%.

Other Cancer Types

The original literature review identified and described studies of LRHT for cancers of the bladder,[12,70-72] brain,[73-75] colon/rectum[76-92] and anus,[93] hepatobiliary,[94-97] lymphatic system (Hodgkin's lymphoma)[98], lung[21,22,27,99-109], skin (melanoma),[17,18,110-113] ovary,[114-120] pancreas,[9,121-129] prostate,[130-133] and vagina and vulva,[134] as well as studies including mixed cancer types. Detailed descriptions for each cancer can be found in the complete monograph.

Quality of Life (QoL) and Symptom Management

Relatively few studies included QoL endpoints,[27,29,38,50,79,90,91,105,106,115] and many were single-arm trials, making interpretation challenging. Two RCTs reported improvements in QoL; in patients with cervical cancer, fatigue, cognitive, and social functioning improved,[29] and in patients with non-small cell lung cancer (NSCLC), physical, emotional, and global QoL as well as symptoms of pain, fatigue, nausea, shortness of breath, and appetite loss significantly improved.[27] Three single-arm trials[38,79,90] and one chart review[106] reported reductions in pain. However, one retrospective study reported increases.[105] Two studies found no change in QoL.[91,115] Ultimately, based on limited data, QoL support is not a primary or recommended indication for use.

Safety

Adverse Events

Locoregional HT is generally safe and well tolerated,[135,136] especially with contemporary technology.[5] Toxicity in patients receiving chemo- and/or RT, with or without LRHT, is typically comparable.[135] Technology advances, treatment planning, and guideline availibility[137-140] have improved tolerability.[5] Thus, safety and toxicity concerns from older studies should be interpreted judiciously. The following AEs have been attributed to HT in recent years (post-2000): discomfort during treatment,[60,63,78,79] mild pain,[25,62,123,135] local erythema,[32,62,66,67] skin/superficial burn (mild-moderate; grade 1–2),[29,13,56,135] and, less commonly, subcutaneous thermal injury/adipose burns.[9,133,30]

There are several cardiorespiratory effects specifically observed with deep regional HT that may affect safety. Changes include slightly increased core temperature (38.2±1.4 vs 36.6±0.8, $p < 0.001$), tachycardia (104±15 vs 85±16 bpm, $p < 0.05$), decreased respiratory rate (23±3 vs 21±3/min, $p < 0.05$), transient orthostatic hypotension after completion of treatment, reduced oxygen saturation (95±2% vs. 97±1%, $p < 0.05$), and fluid loss through sweating when compared with baseline.[141]

Interactions

Other Cancer Therapies: Locoregional HT is considered a chemosensitizer and radiosensitizer[5] and is regularly used with chemotherapy and radiation as reviewed above. There is insufficient evidence for the combined use of HT with targeted therapies including monoclonal antibodies and small molecule inhibitors, or endocrine therapies.

Other Medications: Locoregional HT should be used cautiously with medications that can alter a patient's consciousness, pain perception, or ability to communicate.

Other Complementary and Alternative (CAM) Therapies: No reports of negative interactions for LRHT and other CAM treatments were found.

Cautions and Contraindications

Common contraindications include:[142,143]

- Patients with implanted/worn/carried medical devices, implants, or any foreign objects
- Inability to feel or respond to pain, including sedation, loss of consciousness, and severe neuropathy
- Systemic fever > 38°C[140]
- Severe pulmonary disease (Forced Expiratory Volume (FEV) < 50%)
- Cardiovascular high-risk patients
- Severe cerebrovascular disease
- Treatment delivered to areas of prior irradiation
- Known decreased circulation in heated area
- Patients prone to hemorrhage, presence of an open wound
- Patients with organ transplant
- Children (due to lack of evidence)

DISCUSSION

Locoregional HT for cancer care can be found in a few North American complementary health clinics, most often offered by naturopathic doctors. Despite the rich research landscape of HT, a comprehensive review of all cancer types was not identified. This review describes the cancers with the strongest evidence for benefit with adjunctive LRHT. There is some encouraging evidence for improvements in OBJR rates, and conceivably survival, for patients with certain cancer types, while in other areas the evidence is preliminary and/or too heterogeneous to form conclusions.

For patients with locally recurrent breast cancer receiving radiotherapy, the addition of HT likely improves CR rates and disease control based on results of a meta-analysis.[11] Less is known about the use and effects of LRHT for patients with different breast cancer presentations (e.g., metastatic disease). For cervical cancer, there is consistent and strong evidence that the addition of LRHT to radiation therapy and chemoradiation for patients with stage II–IVa disease is beneficial. Further studies are needed to determine the magnitude of effect and impact on unique subgroups of patients who may benefit. For patients with esophageal cancer, results are suggestive of benefit for response rate and survival outcomes when combined with neoadjuvant conventional care. Although results were consistent across studies, the quality of the RCTs was generally low. Locoregional HT is a promising treatment to improve survival in advanced gastric cancer and as a neoadjuvant treatment for operable gastric cancer. Combined with RT, HT may improve response rates in patients with locally advanced HNC based on controlled trials, and further research is warranted for combination with CRT. Evidence demonstrates a benefit for PFS and OS in patients with localized, high-risk STS treated with neoadjuvant and adjuvant LRHT with chemotherapy compared with chemotherapy alone. The evidence for the use of HT in other settings with sarcomas or other soft-tissue tumours is unclear.

Treatment methods including timing of LRHT in relation to conventional treatment, frequency, and duration are important clinical considerations. Quality assurance guidelines for HT state that chemotherapy is to be given just before or simultaneous to HT, and radiation be given ideally within one hour of HT (but up to four hours is acceptable).[138] This guideline is consistent with the methods used by almost all studies. The target tumour temperature ranges for LRHT are 39°C to 45°C, however 41°C to 43°C is considered optimal.[4,5] Based on RCTs (Table 2), LRHT is most commonly administered once or twice weekly for the duration of conventional treatment, with each session typically lasting 60 to 90 minutes.[140]

Multiple theories of mechanism of action exist for HT, including mitigating hypoxia and inflammation via perfusion and oxygenation changes,[3] damaging tumour vasculature,[3] and denaturing structural proteins.[144] Synergistic effects with chemotherapy include increasing cell membrane permeability and drug uptake by malignant cells[3] and enhancing chemotherapeutic cytotoxicity.[145] When combined with radiation, HT may offset hypoxia-associated radioresistance,[136] suppress cancerous DNA damage repair,[136] and augment advantageous proapoptotic effects[3] and reactive oxygen species.[136]

The studies included in this review have several limitations. First, most of the studies were single-arm or observational. These studies have a greater risk of bias as they lack controls and blinding, making it difficult to determine the effect of the LRHT compared with the other treatments. Many of the studies had small samples sizes, in some cases fewer than 10 people. Again, this weakens the strength of the conclusions and often leaves the studies underpowered to detect clinical outcome changes. Technology has significantly changed in the past two decades, with studies published prior to 2000 often reporting higher AE rates and not always having proper treatment planning or the ability to achieve target temperature and duration.[4,5] In addition, changes to conventional care within contemporary settings may not reflect the standards of care provided in some older trials, rendering them not comparable/relevant.

There are several limitations to this review. First, a rigorous evaluation and quality assessment including risk of bias using a validated tool was not performed. Although some qualitative description of trial quality was provided, without a standardized approach, some poorer-quality studies may have been overrepresented and, alternatively, higher-quality studies not given sufficient attention. Second, the quality and types of studies included have a high degree of population and co-treatment heterogeneity, making interpretation and comparison of results challenging. Lastly, due to the sheer number of studies included, a full description of the trials and outcomes could not be practically provided. In addition, the heterogeneity and scope of the work performed did not allow for meta-analysis.

Moving forward, high-quality RCTs are necessary for most cancer types to assess the efficacy and magnitude of the effect of LRHT and create changes to practice. Future studies should be sufficiently powered with a large enough sample size to enable the clinical effect to be observed, low risk of bias with proper randomization including allocation concealment, and the appropriate population type, as well as proper quality assurance of

treatment application. Additionally, studies using LRHT alongside newer cancer treatments, including immunotherapy, monoclonal antibodies, and tyrosine kinase inhibitors, are needed as these therapies are being increasingly used in oncology.[146,147]

Data Sharing Statement

Additional information, including access to the complete monograph, is available upon request. Please contact Dugald Seely, ND, MSc at dseely@thechi.ca.

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We have read and understood the *CAND Journal's* policy on conflicts of interest disclosure and declare that we have none.

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