



DOSSIER · THERAPY

# Hyperthermia

**Hyperthermia** refers to the targeted overheating of body tissue or the entire organism. The body of evidence in humans is extensive. The primary focus lies in oncology, though the methodological heterogeneity of the studies limits comparability.

**1,669**

STUDIES IN  
TOTAL

**1,072**

IN HUMANS

**347**

OF WHICH  
CONTROLLED

**38**

IN ANIMALS

**82**

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-04

## How to Read This Dossier

### ESTABLISHED

measured in humans, with a comparison group

### PLAUSIBLE

supported by mechanism, animal studies or observation

### HYPOTHESIS

a likely connection that still needs to be tested

# Hyperthermia at a Glance

## ORIGIN:

Hyperthermia is a physical therapy method in which body tissue or the entire organism is deliberately heated to 39–45 °C. Historically used in antiquity, modern applications were developed in the 20th century. Today, it is primarily employed in oncology, combined with radiotherapy or chemotherapy, as well as for chronic inflammation or pain syndromes. The procedure is performed locally, regionally, or systemically, with temperature monitoring to avoid tissue damage.

## EVIDENCE BASE:

426 evaluated studies · 68 controlled human trials · 161 observational studies · 24 review articles · 9 animal studies · 17 cell culture studies

## STRONGEST EVIDENCE:

- **Oncology** A Phase II study involving 40 patients with advanced soft tissue sarcomas showed an objective response rate of 37% using regional hyperthermia combined with chemotherapy. No increased toxicity was observed, but the lack of a control group limits conclusiveness.
- **Oncology (Cervical Carcinoma)** A meta-analysis revealed a 22% higher complete remission rate and 23% improved locoregional control with hyperthermia plus radiotherapy compared to radiotherapy alone, without increased toxicity. Heterogeneous protocols limit comparability.
- **Depression** A randomised study with 30 patients showed a reduction in depressive symptoms after a single whole-body hyperthermia session over 6 weeks. The small sample size and lack of long-term data limit generalisability.
- **Skin (Cutaneous Leishmaniasis)** Local heat therapy (50 °C) showed efficacy comparable to systemic antimonials for cutaneous leishmaniasis, with fewer systemic side effects. Small sample sizes and short follow-up periods were limitations.
- **Cardiovascular (Peripheral Arterial Disease, pAVK)** Heat therapy showed improved walking distance and lowered blood pressure in peripheral arterial disease similarly to exercise therapy. Small sample size and lack of a control group were limitations.

## LIMITATIONS:

- Methodological heterogeneity (local vs. systemic hyperthermia, temperature ranges, combination therapies) complicates meta-analyses and standardisation.
- Data on non-oncological applications (e.g., depression, dysmenorrhoea) are less consistent and often of lower methodological quality.
- Long-term data on side effects, secondary effects, or quality of life are lacking, particularly for oncological combination therapies.

## CLASSIFICATION:

Hyperthermia is a versatile physical therapy with proven efficacy in oncology and initial indications of benefit for depression, pain syndromes, and cardiovascular diseases. However, its broad clinical application is limited by methodological heterogeneity and a lack of long-term data.

## 1. What Hyperthermia Is

**Hyperthermia** is a physical therapy method in which tissue or the whole body is heated to temperatures between 39 °C and 45 °C. Application can be local (e.g., via microwaves, ultrasound, or radiofrequency), regional (e.g., for peritoneal carcinomatosis), or systemic (whole-body hyperthermia). Historically, the use of heat in medicine dates back to antiquity, but modern techniques were only developed in the 20th century. Today, hyperthermia is primarily investigated in combination with radiotherapy or chemotherapy but is also used as a standalone treatment for chronic inflammation or pain syndromes.

**Implementation** varies depending on the objective: local hyperthermia targets tumour tissue, while whole-body hyperthermia affects the entire organism. Temperature is controlled via sensors to prevent tissue damage. A key mechanism is the **heat shock response**, in which cells produce proteins to protect against thermal stress. In oncology, the increased blood flow and oxygen supply to tissue are utilised to enhance the effects of chemotherapy or radiotherapy. However, the **diversity of methods** complicates standardisation and comparability of studies.

## 2. What the Studies Show in Detail

The key human studies and most important reviews—by application area, including population, duration, preparation, outcome measures, and results as reported in the original publications. Numbers are only included where the study provides them.

Distribution of **controlled human trials** by application area—numbers are not additive, as a single study may be assigned to multiple areas:

| APPLICATION AREA | CONTROLLED STUDIES |
|------------------|--------------------|
| Oncology         | 36                 |

| APPLICATION AREA        | CONTROLLED STUDIES |
|-------------------------|--------------------|
| Safety and Tolerability | 32                 |
| Musculoskeletal System  | 10                 |
| Gut and Microbiome      | 9                  |
| Immune System           | 7                  |
| Heart and Circulation   | 7                  |
| Metabolism              | 5                  |
| Fatigue and Stress      | 5                  |

## Cognition and Mental Health

In a randomised, double-blind, placebo-controlled study, the efficacy of a single whole-body hyperthermia (WBH) session was investigated in patients with major depressive disorder (MDD). The primary endpoint was the change in depressive symptoms after 6 weeks, measured using the Hamilton Depression Rating Scale (HDRS-17). The effect persisted throughout the observation period, though the sample size was small ( $n = 30$ ), and long-term effects beyond 6 weeks were not examined. The study showed a specific antidepressant effect of WBH, but data on reproducibility and potential neurobiological mechanisms are lacking.

**HYPOTHESIS** The study suggests that WBH may act via thermoregulatory or immunomodulatory mechanisms, as hyperthermia influences the release of heat shock proteins and proinflammatory cytokines. However, whether these effects directly correlate with the antidepressant response remains speculative, as no biomarkers or neurophysiological parameters were assessed. Furthermore, it is unclear whether repeated WBH sessions enhance the effect or whether a combination with psychotherapy or pharmacotherapy would act synergistically.

## Oncology

A Phase II study <sup>(1)</sup> investigated the combination of regional hyperthermia (RHT) with ifosfamide and etoposide in 40 patients with advanced soft tissue sarcomas (25 soft tissue sarcomas, 8 Ewing sarcomas, 3 osteosarcomas, 4 chondrosarcomas). Patients received a mean of 6.6 RHT sessions (265 treatments in total) combined with chemotherapy (ifosfamide 1.5 g/m<sup>2</sup> on days 1–5, etoposide 100 mg/m<sup>2</sup> on days 1, 3, and 5). The objective response rate was 37% (6 complete remissions, 4 partial remissions). The study provides no evidence for the isolated effect of RHT, as RHT was always administered alongside chemotherapy, and the design lacked a chemotherapy-only control group.

The OVHIPEC-2 study <sup>(2)</sup> is an ongoing, international, randomised Phase III trial involving 538 planned patients with FIGO stage III epithelial ovarian cancer. Following complete or near-complete (residual tumour  $\leq 2.5$  mm) primary cytoreduction, patients are randomised 1:1 to receive either hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m<sup>2</sup> at 40 °C for 90 minutes) or no HIPEC. All patients subsequently receive 6 cycles of platinum-paclitaxel chemotherapy. The primary endpoint is overall survival. The study aims to determine whether HIPEC provides a survival benefit in primary cytoreduction, following earlier studies (e.g., OVHIPEC-1) that demonstrated this for interval cytoreduction after neoadjuvant chemotherapy. A critical limitation is that the study is open-label, increasing the risk of bias, and that the HIPEC methodology (temperature, duration, chemotherapeutic agent) is not standardised.

A systematic review with meta-analysis <sup>(3)</sup> examined the combination of locoregional hyperthermia (HT) with radiotherapy (RT) and/or chemotherapy (CT) in locally advanced cervical cancer (FIGO IIB–IVA). The combination of HTRT ( $n = 215$ ) vs. RT alone ( $n = 212$ ) showed a 22% higher rate of complete remissions ( $p < 0.001$ ) and a 23% higher locoregional control ( $p < 0.001$ ). A non-significant survival benefit of 8.4% in favour of the HTRT group was observed, with no differences in acute or late toxicities. A limitation is that the studies were heterogeneous (different HT protocols, RT doses, CT regimens) and lacked long-term data on toxicity and quality of life.

A subgroup analysis of the EORTC-62961 study <sup>(6)</sup> investigated the effect of regional hyperthermia (RHT) in addition to chemotherapy (EIA: etoposide, ifosfamide, doxorubicin) in 149 patients with macroscopically completely resected (R0/R1) abdominal or retroperitoneal high-risk sarcomas. The RHT group ( $n = 76$ ) received a mean of 5 cycles of EIA + RHT, while the control group ( $n = 73$ ) received 5 cycles of EIA alone. At 5 years, locoregional recurrence-free survival (56% vs. 45%,  $p = 0.044$ ) and disease-free survival (34% vs. 27%,  $p = 0.040$ ) were significantly better in the RHT group, whereas overall survival showed no difference (57% vs. 55%,  $p = 0.82$ ). Toxicity was comparable in both groups, though the study was not primarily designed for this subgroup, and the sample size was limited. Additionally, data on quality of life and long-term functional impairment due to RHT are lacking.

A randomised Phase II study <sup>(9)</sup> compared the combination of intravenous vitamin C (IVC, 1 g/kg/day) and modulated electrohyperthermia (mEHT, 3× per week for 25 sessions) plus best supportive care (BSC) with BSC alone in 97 patients with refractory advanced non-small cell lung cancer (NSCLC). After a median follow-up of 24 months, the combination group showed significantly longer progression-free survival (3 vs. 1.85 months,  $p < 0.05$ ) and overall survival (9.4 vs. 5.6 months,  $p < 0.05$ ). The disease control rate at 3 months was 42.9% vs. 16.7% ( $p <$

0.05). Quality of life improved in the active group despite the advanced stage. A limitation is that the study was not blinded, and the additive effect of IVC and mEHT could not be isolated, so the contribution of hyperthermia alone to these outcomes remains unclear. Furthermore, data on immune modulation or biomarkers to explain the mechanism of the combination are lacking.

A randomised Phase III study (<sup>10</sup>) investigated the addition of modulated electrohyperthermia (mEHT) to chemoradiotherapy in 202 patients with locally advanced cervical cancer. The study explored whether mEHT may enhance systemic immune responses, such as through the induction of heat shock proteins or the release of tumour antigens, but these endpoints were exploratory and not confirmed as clinical outcomes. The potential abscopal effect was not investigated as a primary endpoint. Additionally, data on the long-term impact on survival are lacking.

## Metabolism

The Prodiges-7 study is a randomised Phase III trial that examined the benefit of hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin (OX) in addition to cytoreductive surgery (CRS) for colorectal peritoneal carcinomatosis. The study was not designed to evaluate the effect of hyperthermia alone on locoregional control, and the observed outcomes may have been influenced by the chemotherapeutic agent, the high glucose concentration in the HIPEC solution (50 g/L), or other procedural factors. The study raises questions about the optimal HIPEC methodology, particularly regarding the choice of chemotherapeutic agent, temperature, and duration of application.

## Skin

A randomised controlled trial (<sup>4</sup>) compared the efficacy of local thermotherapy (ThermoMed device, 50 °C for 30 seconds) with intravenous sodium stibogluconate (SSG, 20 mg/kg/day for 10 doses) in 54 patients with cutaneous *Leishmania major* infection. After 2 months, there was no significant difference in the cure rate (54% SSG vs. 48% ThermoMed,  $p = 0.78$ ), though the per-lesion cure rate was higher in the ThermoMed group (73% vs. 59%,  $p = 0.053$ ). ThermoMed treatment was associated with local side effects such as blistering and erythema, while SSG caused systemic toxicities (e.g., pancreatitis, arthralgia). A limitation was the small sample size and the short follow-up period of 12 months. The study suggests that local thermotherapy may be an effective and less toxic alternative to systemic antimonials, particularly for uncomplicated lesions.

A randomised study (<sup>8</sup>) compared the efficacy of local thermotherapy using radiofrequency (RF, 50 °C for 30 seconds, once per week for 4 weeks) with intralesional meglumine antimoniate injection (once per week for 4 weeks) in 117 patients with cutaneous leishmaniasis. After 6 months, the RF group showed a higher rate of complete cures (80.7% vs. [data incomplete]). The RF treatment was associated with fewer systemic side effects but more frequent local reactions such as blistering. A limitation was that the study was not blinded, and the follow-up period was limited to 6 months. The results indicate that RF may be an effective and safe alternative to antimonials, particularly in regions with high resistance rates to antimonials.

## Heart and Circulation

A randomised controlled trial (<sup>5</sup>) compared the effects of thermotherapy (3–5× per week for 12 weeks, 30 minutes at ~39 °C in a thermal bath followed by 30 minutes of gymnastics) with supervised exercise training (1–2× per week for 90 minutes) in 22 patients with peripheral arterial occlusive disease (PAOD). Both groups showed a significant improvement in walking distance in the 6-minute walk test (increase of 41 m,  $p = 0.006$ ) and pain-free walking distance (increase of 43 m,  $p < 0.001$ ). Systolic blood pressure decreased more in the thermotherapy group (-7 mmHg vs. -3 mmHg,  $p < 0.001$ ). The study suggests that thermotherapy may be an effective alternative to exercise therapy, particularly for patients with limited mobility. A limitation was the small sample size and the lack of a control group without intervention. Additionally, compliance was not systematically recorded, and long-term effects were not investigated.

A systematic review with meta-analysis (<sup>18</sup>) examined the effect of various thermotherapy modalities (e.g., sauna, thermal bath, local heat application) on blood pressure and vascular function. The review included fifteen studies involving healthy and clinical populations, but the analysis was heterogeneous regarding the type and duration of thermotherapy. The findings suggest potential benefits of thermotherapy, though long-term data on sustainability and effects in specific patient groups (e.g., hypertensive patients with comorbidities) are lacking.

## Further Investigations

A systematic review with meta-analysis (<sup>7</sup>) examined the efficacy of thermotherapy in primary dysmenorrhoea. Three studies comparing heat pads with analgesics showed a significant pain reduction in favour of thermotherapy (standardised mean difference: -0.72, 95% CI: -0.97 to -0.48,  $p < 0.001$ ). One study comparing thermotherapy with no treatment showed a significant pain reduction (mean difference: -4.04 VAS points,  $p < 0.001$ ). However, the studies were of low methodological quality (mean PEDro score: 4.8/10) and heterogeneous regarding the type of thermotherapy (e.g., heat pads, heat patches) and duration of application. Additionally, data on quality of life and long-term efficacy are still lacking.

A systematic review summarised the evidence on thermotherapy for primary dysmenorrhoea. Three studies on thermotherapy showed a significant reduction in pain, though none of the studies were blinded, and the sample sizes were small ( $n < 50$  per study). The methodological quality was moderate (mean PEDro score: 6.3/10). None of the studies examined quality of life as an endpoint. The review concludes that thermotherapy may be a promising adjuvant for pain relief, but high-quality studies with standardised protocols and longer follow-up periods are lacking.

## Bowel and Microbiome

A review <sup>(17)</sup> discusses the effects of heat and physical exertion on intestinal barrier function and tight junction proteins. Hyperthermia (both passive and exercise-induced) can lead to increased intestinal permeability in humans, associated with reduced expression of tight junction proteins such as occludin and claudin-1. Preclinical studies in animals suggest that heat stress may trigger an inflammatory response in the gut, mediated by the release of cytokines such as TNF- $\alpha$  and IL-6. This inflammatory response has not been investigated in humans. Increased permeability has been observed after extreme physical exertion (e.g., marathon running) or passive hyperthermia (core temperature >39 °C) in healthy subjects, but the clinical relevance remains unclear, particularly for patients with inflammatory bowel disease or other gastrointestinal conditions.

## Inflammatory Processes

An observational study <sup>(16)</sup> investigated the role of the cellular stress response (heat shock response) in the pathogenesis and treatment of type 2 diabetes mellitus (T2DM). A 3-week intervention with daily hyperthermia (hot water bath, 30–60 minutes at 39–40 °C) in T2DM patients showed a 1% reduction in HbA1c levels, a trend towards weight loss, and an improvement in symptoms of diabetic neuropathy. The study suggests that hyperthermia may enhance the expression of heat shock proteins, but the small sample size (n = 14) and the lack of a control group limit the conclusions. Furthermore, no long-term data were collected, so it remains unclear whether the effects are sustainable. The findings indicate that hyperthermia may act as an adjuvant therapy in T2DM, but randomised controlled trials with larger samples and longer follow-up periods are needed.

## Overall Picture

The available studies demonstrate that hyperthermia shows potential efficacy across various medical fields, though the strength of evidence varies considerably. The most consistent data exist in oncology, particularly for the combination of hyperthermia with chemotherapy or radiotherapy in locally advanced tumours (e.g., cervical cancer, soft tissue sarcomas, ovarian cancer). Several randomised studies showed improved locoregional control and, in some cases, overall survival, though the results are not consistent (e.g., conflicting data on HIPEC in ovarian cancer). In psychiatry and neurology, there are initial indications of an antidepressant effect of whole-body hyperthermia, but replicative studies and long-term data are lacking. In cardiovascular and metabolic medicine, promising effects on blood pressure, vascular function, and insulin sensitivity have been observed in small, heterogeneous studies.

The evidence is considerably weaker in other areas such as dermatology (e.g., cutaneous leishmaniasis), gynaecology (dysmenorrhoea), or gastroenterology (intestinal barrier function). Here, most recommendations are based on small, often unblinded studies with short follow-up periods. Furthermore, data on patient-relevant endpoints such as quality of life or long-term toxicity are frequently lacking. A central issue is the lack of standardisation in hyperthermia protocols (temperature, duration, mode of application), which complicates the comparability of studies. Overall, hyperthermia appears to be a versatile procedure with potential applications across various specialties, but further high-quality studies are needed to confirm its efficacy and safety in individual indications.

### Methodology of the Study Landscape

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#### THE STUDIES ON HYPERTHERMIA

encompass a broad spectrum of designs, ranging from controlled human trials to observational studies and systematic reviews. Among the controlled human trials, the duration of the intervention varies considerably: from single sessions (e.g., whole-body hyperthermia for depression) to multi-week protocols (e.g., regional hyperthermia for sarcomas with 6–8 sessions over 4–6 weeks). Primary endpoints frequently include response (complete/partial remission), progression-free survival, or overall survival. In non-oncological controlled studies (e.g., psychiatry, cardiology), surrogate parameters such as depressive symptoms (HDRS-17), blood pressure, or vascular function (FMD) are often assessed. Systematic weaknesses include the lack of blinding (particularly in local hyperthermia), small sample sizes, and short follow-up periods. Additionally, dose-finding studies are often lacking, leaving uncertainty about the optimal temperature, duration, and frequency of hyperthermia. Another deficit is the absence of biomarker studies that could elucidate the mechanism of action of hyperthermia (e.g., immune modulation, heat shock protein induction).]

### Hyperthermia in Oncology: Combination Partner or Standalone Therapy?

#### ONCOLOGICAL HYPERTHERMIA

is almost exclusively investigated in combination with chemotherapy or radiotherapy. The **rationale** is based on the assumption that heat enhances the effects of these treatments, for example, through increased blood flow or oxygen supply to tumour tissue. However, **controlled studies present an inconsistent picture**: some report improved response rates, while others find no significant advantage over standard therapy alone. The **methodological quality** varies considerably, particularly in older studies.

#### A CENTRAL ISSUE

is the lack of standardisation in hyperthermia procedures. Temperature, duration, and mode of application (local, regional, systemic) differ across studies, complicating direct comparisons. Furthermore, many studies are **monocentric** and conducted with small sample sizes. **HIPEC research** (hyperthermic intraperitoneal chemotherapy) exemplifies these contradictions: while some studies suggest a survival benefit, others conclude that the benefit does not justify the increased burden on patients. The **question of the independent efficacy** of hyperthermia thus remains unanswered.

### 3. How Robust the Research Is

Research on hyperthermia focuses on **oncological applications**, which constitute a significant portion of controlled human studies. Other key areas include **safety aspects**, the **musculoskeletal system**, as well as the **gut, immune system**, and **cardiovascular system**. Most studies are observational, with controlled trials being less common. Systematic reviews and mechanistic studies complement the evidence base, though the latter are often conducted at the cellular or animal experimental level. **Citation frequency** indicates that oncological combination therapies (e.g., HIPEC) and the treatment of depression are particularly intensely discussed.

The **robustness** of the data is limited by methodological differences. While controlled studies exist, the **heterogeneity** of procedures (local vs. systemic hyperthermia, varying temperature ranges, combination partners) complicates meta-analyses. Most studies in the evidence base are observational, which restricts their generalisability to broader clinical practice. Additionally, long-term data on side effects or secondary effects are often lacking. The **most-cited studies** reflect an interest in combination strategies, though not all demonstrate a clear advantage over standard therapies. The **evidence base for non-oncological applications** (e.g., depression, dysmenorrhoea) is smaller and less consistent, with controlled trials being particularly sparse.

### 4. Common Claims — and What the Data Show

| STATEMENT                                               | STUDY EVIDENCE                                                                                                                                |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Hyperthermia as a standalone cancer therapy             | The available data is limited to combination methods. Controlled studies on standalone application are lacking or show insufficient evidence. |
| Whole-body hyperthermia for depression                  | A frequently cited study demonstrates effects, yet replications or long-term data are still emerging. The evidence base is limited.           |
| Hyperthermia for chronic inflammation                   | Observational studies suggest associations, yet controlled studies are rare and methodologically heterogeneous.                               |
| Local hyperthermia for infections (e.g., leishmaniasis) | Individual controlled studies demonstrate efficacy, yet the transferability to other pathogens or clinical settings remains unclear.          |

### 5. The Most Robust Studies

Ranked by evidential strength, not by prominence. The full evaluation includes significantly more studies; here, only the most reliable are listed.

#### Controlled Human Studies

- Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder: A Randomized Clinical Trial (2016)
- <sup>1</sup> Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas: a phase II study (1990)

- <sup>2</sup> Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for FIGO stage III epithelial ovarian cancer: OVHIPEC- (2020)
- HIPEC with oxaliplatin for colorectal peritoneal metastasis: The end of the road? (2019)
- <sup>3</sup> Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta (2016)
- <sup>4</sup> A randomised controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous Leishmania major infection (2010)
- <sup>5</sup> Heat therapy vs. supervised exercise therapy for peripheral arterial disease: a 12-week randomised, controlled trial (2019)
- <sup>6</sup> Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection (2014)
- <sup>7</sup> Heat therapy for primary dysmenorrhoea: A systematic review and meta-analysis of its effects on pain relief and quality of life (2018)
- <sup>8</sup> Efficacy of local heat therapy via radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate (2007)
- HIPEC Methodology and Regimens: The Need for an Expert Consensus (2021)
- TENS and heat therapy for pain relief and quality of life improvement in individuals with primary dysmenorrhoea: A systematic review (2016)
- Hyperthermic intraperitoneal chemotherapy does not improve survival in advanced ovarian cancer (2019)
- Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer (2013)
- <sup>9</sup> A randomised phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell [lung cancer] (2020)
- <sup>10</sup> Potentiation of the abscopal effect by modulated electro-hyperthermia in patients with locally advanced cervical cancer (2020)
- Radiotherapy for melanoma: More than DNA damage (2019)
- Hyperthermic intraperitoneal chemotherapy for epithelial ovarian cancer: A meta-analysis (2022)
- <sup>11</sup> Ifosfamide, carboplatin and etoposide (ICE) combined with 41.8 °C whole-body hyperthermia in patients with refractory sarcoma (1996)
- <sup>12</sup> Chemoradiotherapy combined with regional hyperthermia for advanced oesophageal cancer: A systematic review and meta-analysis (2017)
- <sup>13</sup> The regimen of gemcitabine and cisplatin combined with radiofrequency hyperthermia for advanced non-small-cell lung cancer: A phase II study (2011)
- Effects of Class IV laser therapy on fibromyalgia impact and function in women with fibromyalgia (2013)
- <sup>14</sup> Heat therapy shows benefit in patients with type 2 diabetes mellitus: A systematic review and meta-analysis (2021)
- <sup>15</sup> Clinical trial protocol for PanDox: A phase I study of targeted chemotherapy delivery to non-resectable primary pancreatic tumours using thermosensitive [liposomal doxorubicin] (2023)

## 6. Summary

Hyperthermia shows promise as an adjunctive measure in oncology, particularly when combined with radiotherapy or chemotherapy. Studies indicate improved response rates and locoregional control in cervical cancer, soft-tissue sarcomas, and peritoneal carcinomatosis, without increased toxicity. For non-oncological applications such as depression or dysmenorrhoea, there are initial indications of efficacy, though these are based on small sample sizes and methodological weaknesses. Further confirmation is required. The evidence regarding cardiovascular effects or dermatological conditions also shows potential but remains insufficient for broad clinical recommendation.

**HYPOTHESIS** The oncological effects may stem from increased perfusion, oxygenation, and heat-shock protein induction, which enhance tumour cell sensitivity to therapies. In depression, thermoregulatory or immunomodulatory effects (e.g., cytokine release) may play a role, though the precise mechanisms remain unclear. For non-oncological applications such as dysmenorrhoea or peripheral arterial disease (PAD), pain relief may be mediated by localised perfusion enhancement or muscle relaxation. **Hypothesis:** Combination strategies (e.g., hyperthermia plus immunotherapy) could act synergistically, but this requires further investigation. Standardised protocols would be necessary to improve comparability and develop clinical guidelines.

Future studies must address the following questions: 1) Which temperature ranges, application durations, and combination partners are optimal for specific indications? 2) How do repeated hyperthermia sessions affect long-term outcomes and quality of life? 3) Which biomarkers or neurophysiological parameters correlate with efficacy, particularly in depression or immunomodulation? 4) Can standardised protocols reduce study heterogeneity and enable meta-analyses? 5) How does hyperthermia compare with or complement established therapies (e.g., psychotherapy, exercise therapy)?

## 7. Unresolved Issues

- **Standardisation:** The lack of uniform protocols for temperature, duration, and mode of application complicates the comparability of studies.
- **Long-term effects:** Data on secondary effects or late sequelae of hyperthermia procedures are scarce.
- **Non-oncological applications:** The evidence for depression, dysmenorrhoea, or cardiovascular effects is fragmentary and often contradictory.

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## Frequently Asked Questions

### Is hyperthermia established as a supportive measure in oncology?

Hyperthermia is used in specialised centres as a **combination partner** with chemotherapy or radiotherapy, particularly in locally advanced tumours or peritoneal carcinomatosis. However, the **evidence base** does not consistently demonstrate superiority over standard therapies. The **S3 guidelines** for certain tumour entities (e.g., cervical carcinoma) mention hyperthermia as an option but do not recommend it as a standard. **Application** thus remains an individualised decision, dependent on centre expertise and patient profile.

### What risks are associated with hyperthermia?

The **risks** depend on the mode of application. Local hyperthermia may lead to **tissue damage** or burns, particularly in cases of impaired sensation. **Whole-body hyperthermia** can result in cardiovascular strain, electrolyte imbalances, and heatstroke. While these effects are documented in controlled studies, **long-term data** on late sequelae are lacking. **Safety studies** indicate that severe adverse effects are rare in the examined applications when temperature is closely monitored.

### Is there evidence for hyperthermia in non-oncological conditions?

The **evidence base** here is considerably weaker. A controlled study on **whole-body hyperthermia for depression** shows effects, but replications are lacking. For **primary dysmenorrhoea**, meta-analyses suggest **pain reduction**, though study quality is heterogeneous. **Cardiovascular effects** (e.g., blood pressure reduction) are discussed in review articles, but the underlying studies are often small and methodologically limited. **Application** outside oncology thus remains experimental.

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