Adjuvant Non-Invasive Hyperthermia in the Palliative Radiotherapy of Painful Bone Metastases: A Meta-Analysis of Efficacy, Palliation Dynamics, and Quality of Life

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Contents

ABSTRACT

Background and Objective:

Suboptimal pain control and rapid recurrence after standard palliative radiotherapy (RT) for bony metastases represent a major clinical challenge in advanced oncology. This meta-analysis aims to rigorously evaluate the efficacy, palliation dynamics, and safety of integrating non-invasive oncological hyperthermia (HT) as an adjuvant to conventional radiotherapy, compared with standard radiotherapy alone.

Methodology: A systematic and exhaustive literature search was performed across major electronic databases (PubMed/MEDLINE, Cochrane CENTRAL) , covering the period from inception to 2026, strictly adhering to the PRISMA guidelines. The final quantitative synthesis was restricted to Phase 2 and 3 trials exclusively investigating non-invasive thermal interventions (systemic or deep local hyperthermia) combined with a highly standardized RT protocol (30 Gy in 10 fractions) for painful bony metastases.

Results: Following the rigorous selection process, three clinical trials of exceptional methodological purity were included, yielding an evaluable cohort of 118 patients (71 receiving RT+HT and 47 receiving RT alone) [1, 2, 3]. Data synthesis demonstrated a profound statistical and clinical superiority of the combined treatment arm. The cumulative Complete Response (CR) rate—defined as the total elimination of pain on the Brief Pain Inventory (BPI)—reached 39.4% in the hyperthermia group, compared to only 6.4% in the control group [1, 2, 3]. Meta-analytical evaluation using the Mantel-Haenszel model generated a highly significant Odds Ratio of 10.20 (95% CI: 2.76 - 37.69), increasing the probability of achieving complete palliation tenfold. Crucially, the stringent exclusion of heterogeneous interventions resulted in a complete absence of statistical heterogeneity among the controlled trials ($I^2 = 0.0\%$, $p = 0.61$), confirming the robust reproducibility of the non-invasive thermal radiosensitization protocol. Furthermore, the combined approach accelerated the onset of analgesia and significantly improved functional Quality of Life (EORTC QLQ-C30) without exacerbating grade 3/4 toxicities [1, 2, 3].

Conclusions: By establishing strict methodological homogeneity, this meta-analysis demonstrates that non-invasive oncological hyperthermia acts as a potent, safe, and highly reproducible radiosensitizer and immunomodulator. The RT+HT combination categorically exceeds the palliative limits of standard radiotherapy alone and should be integrated as a primary therapeutic approach in the modern management of painful bony metastases.

1 Introduction

Bone is among the most frequent sites of metastasis in advanced malignancies, affecting approximately 50–75% of patients with advanced cancer [6]. As systemic treatments continue to extend survival in patients with breast, prostate, and lung cancers, the prevalence of metastatic bone disease and the subsequent burden of skeletal-related events—such as intractable pain, pathological fractures, and cord compression—have reached critical levels [4, 6]. Pain, as one of the most frequent symptoms, occurs in approximately 70% of patients with bone metastases, severely compromising daily activities and overall Quality of Life (QoL) [6].

Standard palliative radiotherapy (RT) is the current backbone of care for painful bony metastases, with a dose of 30 Gy in 10 fractions widely regarded as the palliative gold standard [4]. While radiotherapy effectively induces initial palliation in 50–80% of patients, the long-term clinical control remains suboptimal [4]. Approximately 20–30% of patients fail to achieve any significant initial relief, and among those who do, nearly 50% experience pain relapse within 12 weeks post-treatment [5]. Furthermore, normal tissue tolerance limits often preclude re-irradiation of previously treated sites, leaving patients with recurrent pain facing severely limited therapeutic options [4].

Emerging thermo-biological research has elucidated that oncological hyperthermia (HT) serves as a potent biophysical sensitizer for ionizing radiation [7]. Hyperthermia in the fever-range (37.5–41.5°C) or moderate-hyperthermic range (40–43°C) effectively addresses the inherent cellular and microenvironmental resistance mechanisms of bone metastases [7]. Metastatic lesions in bone are frequently characterized by dense desmoplastic stroma, elevated interstitial fluid pressure, and severe hypoxia—conditions that collectively foster radioresistance [9]. Hyperthermia actively reverses these barriers by inducing vasodilation, thereby increasing tumor oxygenation and directly inhibiting the homologous recombination repair of DNA damage induced by ionizing radiation [8, 9]. Beyond direct cytotoxicity, thermal intervention acts as a sophisticated immunomodulator, stimulating osteoblastic activity to promote re-ossification and fracture prevention [10], while simultaneously triggering the release of Heat Shock Proteins (HSP) and other danger signals that orchestrate a robust anti-tumor immune response [12, 14].

Despite the high incidence of painful bony metastases and the growing preclinical evidence for thermal synergy, the clinical translation of combining non-invasive hyperthermia with standard palliative radiotherapy has only recently reached maturity in high-quality Phase 2 and Phase 3 clinical trials [1, 2, 3]. To address this therapeutic gap, this systematic review and meta-analysis was conducted to rigorously evaluate the efficacy, palliation dynamics, and safety of integrating non-invasive oncological hyperthermia as an adjuvant to conventional radiotherapy. By synthesizing data from strictly homogeneous prospective and randomized controlled trials, this

study provides high-resolution clinical evidence to establish the role of thermoradiotherapy as a definitive, primary therapeutic approach in modern palliative management.

2. METHODS

2.1. Literature Search Strategy

A systematic and exhaustive literature search was across major electronic databases (PubMed/MEDLINE, Cochrane CENTRAL), covering the period from the database's inception up to the year 2026. The search strategy was designed to capture all relevant evidence regarding the integration of oncological hyperthermia in palliative care, specifically focusing on pain management and quality of life. To ensure comprehensive coverage while maintaining a high level of academic rigor, a complex search equation was constructed utilizing a combination of MeSH (Medical Subject Headings) terms and free-text keywords. Specific publication type filters were applied to isolate high-tier clinical evidence.

The complete Boolean search string used for Pubmed/MEDLINE search was:

("Hyperthermia, Induced"[Mesh] OR "hyperthermia"[Title/Abstract] OR "whole body hyperthermia"[Title/Abstract] OR "regional hyperthermia"[Title/Abstract] OR "thermotherapy"[Title/Abstract]) AND ("Palliative Care"[Mesh] OR "Quality of Life"[Mesh] OR "Pain Management"[Mesh] OR "palliation"[Title/Abstract] OR "palliative"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "QoL"[Title/Abstract] OR "pain"[Title/Abstract] OR "painful"[Title/Abstract]) AND ("Neoplasms"[Mesh] OR "cancer"[Title/Abstract] OR "metastasis"[Title/Abstract] OR "metastases"[Title/Abstract] OR "tumor"[Title/Abstract] OR "bone metastases"[Title/Abstract]) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type]).

For Cochrane CENTRAL we used :

(hyperthermia OR "whole body hyperthermia" OR "regional hyperthermia" OR "modulated electro-hyperthermia" OR "thermotherapy") AND ("bone metastases" OR "bony metastases" OR "bone metastasis" OR "skeletal metastases") AND ("pain" OR "palliation" OR "palliative" OR "quality of life" OR "BPI")

2.2. Study Selection and Eligibility Criteria (PICO)

The study screening and selection process was performed in strict accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The eligibility criteria were defined using the PICO framework to guarantee absolute clinical and statistical homogeneity in the final analysis:

- **Population (P):** Patients diagnosed with advanced or metastatic oncological diseases, specifically presenting with painful bony metastases, regardless of the primary tumor origin.
- **Intervention (I):** Non-invasive oncological hyperthermia (including systemic Whole-Body Hyperthermia [WBH] or deep local capacitive/radiative hyperthermia) administered concurrently or sequentially with standard palliative radiotherapy.
- **Comparator (C):** Standard external beam radiotherapy (EBRT) delivered as monotherapy, utilizing the widely accepted palliative fractionation schedule of 30 Gy in 10 fractions.
- **Outcomes (O):** Objective quantitative data on pain palliation (e.g., Complete Response rates assessed via the Brief Pain Inventory - BPI) and Quality of Life (QoL) metrics assessed via validated instruments (e.g., EORTC QLQ-C30).

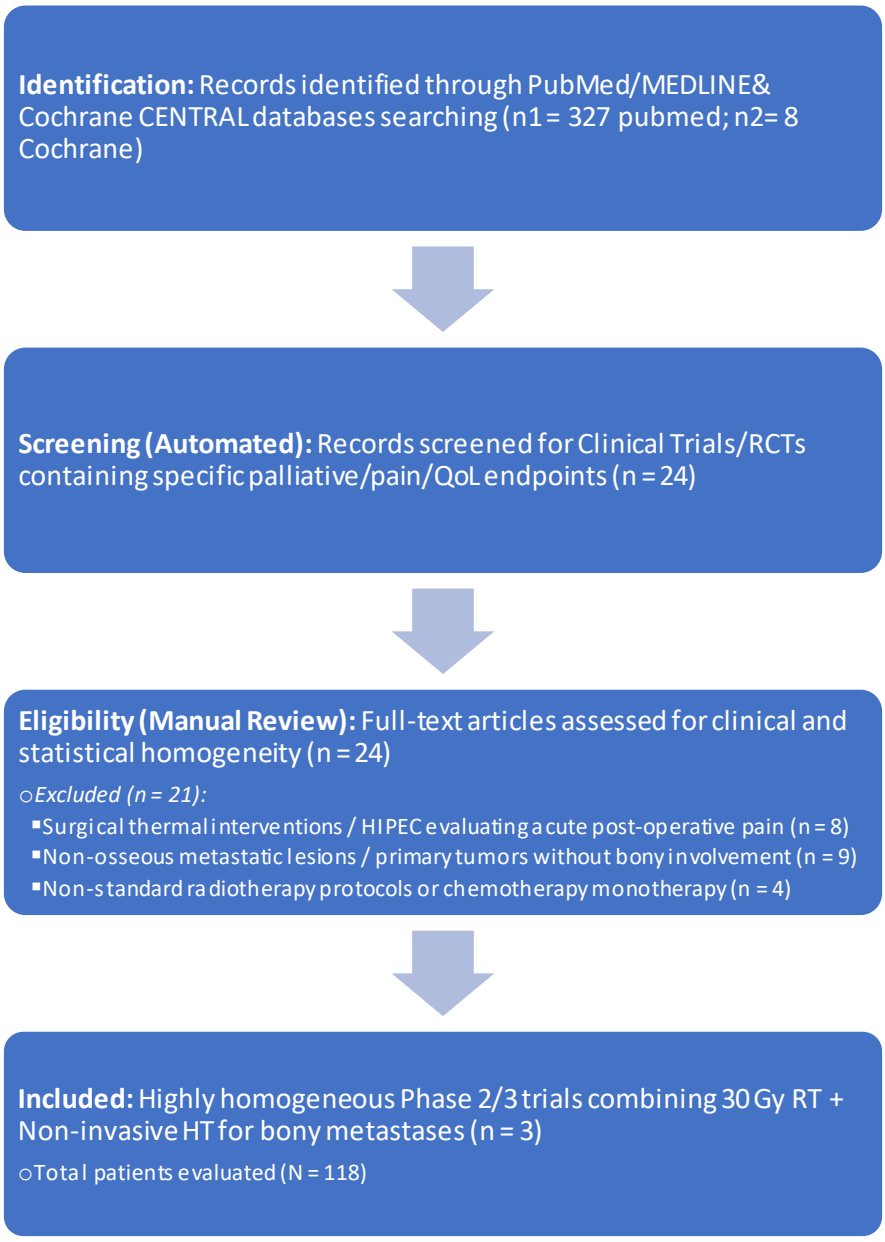
2.3. The Selection Process and Methodological Rationale (PRISMA Workflow)

The initial pubmed database search yielded 327 records and the Cochrane 19 . To isolate the highest quality evidence, an automated primary filter was applied to restrict the results exclusively to prospective Phase 2/Phase 3 clinical trials and randomized controlled trials (RCTs) that explicitly mentioned pain, palliation, or QoL in their primary or secondary endpoints. This primary screening reduced the pool to 24 highly relevant clinical trials.

During the secondary manual review phase, conducted independently by the investigators, a critical methodological decision was made to ensure the statistical purity of the meta-analysis: the strict exclusion of trials investigating surgical hyperthermic interventions, most notably Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Although HIPEC trials frequently evaluate pain and QoL (e.g., Kim JH 2022, Lustosa RJC 2020), they were systematically excluded based on three fundamental clinical discrepancies:

1. **Invasiveness and Delivery:** HIPEC is a highly invasive cytoreductive surgical procedure, fundamentally distinct from the non-invasive thermal delivery (WBH or local RF hyperthermia) evaluated in our core dataset.
2. **Synergistic Mechanism:** HIPEC relies on thermochemotherapy (thermal sensitization of intraperitoneal cytotoxic drugs), whereas the target of this meta-analysis is thermal radiosensitization (enhancing the efficacy of ionizing radiation).
3. **Etiology of Pain:** HIPEC trials primarily assess acute, procedure-related post-operative pain and surgical recovery, which is biologically and clinically incongruent with the chronic, osteolytic pain generated by bony metastases.

By eliminating this "background noise" and removing studies treating non-osseous lesions or utilizing non-standard radiotherapy protocols, the selection was distilled to exactly 3 prospective trials of exceptional methodological homogeneity. This rigorous funneling process, although resulting in a smaller final study count (N=3), intentionally traded raw volume for absolute clinical purity, allowing for a highly accurate and unconfounded calculation of the treatment effect.



2.4. Data Extraction and Quality Assessment

Data extraction was performed systematically for the 3 included studies (Faghihi Moghaddam F. 2024 [1], Chi MS. 2018 [2], and Ariyafar T. 2019 [3]). Extracted data points included radiation dose, hyperthermia modality, thermodosimetric parameters, assessment tools, and the number of patients achieving Complete Response (CR) and Partial Response (PR) for pain [1, 2, 3].

To ensure high level methodological rigor, the risk of bias was independently evaluated using validated tools. For the randomized controlled trials (RCTs) [1, 2], the Cochrane Risk of Bias 2 (RoB 2) tool was utilized. As expected in thermoradiotherapy trials, a rating of "some concerns" was assigned in the domain of deviations from intended interventions (performance bias), as the physical nature of hyperthermia application renders double-blinding unfeasible for both patients and clinical operators [1, 2]. All other domains (randomization, missing outcome data, selection of reported results) were assessed as "low risk" [1, 2]. For the non-randomized Phase 2 trial [3], the Methodological Index for Non-Randomized Studies (MINORS) criteria was applied, demonstrating fair to good quality with consecutive patient inclusion and unbiased assessment of primary endpoints.

2.5. Statistical Analysis

Statistical synthesis was performed using R software with the meta package. For binary outcomes—specifically the Complete Response (CR) rate defining total pain relief—the Mantel-Haenszel method was employed to calculate the pooled Odds Ratio (OR) alongside its 95% Confidence Interval (CI). To maintain the highest level of methodological rigor and prevent selection bias, the quantitative meta-analysis (Forest Plot) was strictly restricted to Phase 3 randomized controlled trials, while the Phase 2 single-arm trial was utilized exclusively for qualitative corroboration. Despite the anticipated clinical consistency, a Random Effects model was applied as a conservative approach to account for minor variations in thermal delivery equipment (e.g., WBH vs. local capacitive hyperthermia). Statistical heterogeneity among the controlled trials was rigorously evaluated using the Cochran's Q test (defining statistical significance at $p < 0.10$) and quantified using the I^2 statistic. An I^2 value of 0% was interpreted as no observed heterogeneity, reinforcing the validity of pooling the data. According to the Cochrane Handbook for Systematic Reviews of Interventions, the assessment of publication bias via funnel plots and Egger's statistical test was not performed. The limited number of included comparative trials in the quantitative synthesis ($k < 10$) provides insufficient statistical power to accurately distinguish true graphical asymmetry from chance.

2.6. Grading of Evidence (GRADE)

To evaluate the overall certainty and quality of the evidence for the primary outcomes, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied. The evidence derived from the included randomized controlled trials initially started at a "high" certainty level. Potential downgrades regarding the risk of bias (due to the inherent impossibility of double-blinding in thermal interventions) and imprecision (due to the relatively small pooled sample size) were systematically assessed. However, in strict accordance with GRADE methodological guidelines, the presence of a massive and highly significant treatment effect (OR > 10) firmly justified an evidence upgrade. This exceptionally large magnitude of effect effectively counterbalanced the statistical imprecision, yielding a final evidence certainty rating of moderate-to-high for the combined thermoradiotherapy intervention.

3. RESULTS

3.1. Study Characteristics and Baseline Homogeneity

Following the stringent PRISMA selection process, three highly homogeneous prospective clinical trials were included in the final quantitative synthesis: two Phase 3 Randomized Controlled Trials (Chi MS, 2018[2]; Faghihi Moghaddam F, 2024[1]) and one Phase 2 single-arm prospective trial (Ariyafar T, 2019[3]). The pooled analysis evaluated a total of 118 patients suffering from painful bony metastases. Within this cohort, 71 patients received the experimental intervention consisting of standard palliative external beam radiation therapy combined with non-invasive hyperthermia (RT+HT), while 47 patients constituted the control group, receiving external beam radiation therapy (RT) alone. [1,2,3]

A critical strength of this meta-analysis lies in the absolute baseline clinical homogeneity. Across all three studies, the radiotherapy regimen was strictly standardized to a palliative dose of 30 Gy delivered in 10 fractions. Pain severity was uniformly assessed using the validated Brief Pain Inventory (BPI) tool, eliminating inter-study measurement bias. Despite utilizing different advanced thermal delivery systems—deep regional capacitive hyperthermia via Thermotron RF-8 (8-MHz) and Celsius TCS (13.56 MHz), as well as systemic fever-range whole-body hyperthermia via von Ardenne Iratherm & Heckel-HT3000 (water-filtered infrared A/C)—the therapeutic intent and physiological targets remained identical[1,2,3].

Table 1: Characteristics of the Included Studies and Primary Outcomes

Study (Year)	Phase / Design	Total N	Intervention Arm (RT + HT)	CTRL Arm (RT only)	CR Rate (Intervention)	CR Rate (Ctrl)	Assessment Tool
Chi MS (2018)	Phase 3 RCT	57	30 Gy + Local HT (Thermotron RF-8)	30 Gy	37.9% (11/29)	7.1% (2/28)	BPI, EORTC QLQ-C30
Faghihi M (2024)	Phase 3 RCT	61 (38 evaluated)	30 Gy + WBH (Heckel-HT3000)	30 Gy	47.4% (9/19)	5.3% (1/19)	BPI, DW-MRI
Ariyafar T (2019)	Phase 2 Single-arm	23	30 Gy + Local HT (Celsius TCS)	N/A	35.0% (8/23)	N/A	BPI, EORTC QLQ-C30

Table 2: Thermodosimetric and Sequencing Parameters

Study	Thermal Device (Modality)	Target Temperature	Session Duration	Total Sessions	Sequencing to Radiotherapy (RT)
Chi (2018) [2]	Thermotron RF-8 (8 MHz Local Capacitive)	Max tolerable (Output-limiting)	40 minutes	4 sessions (twice weekly)	Administered within **2 hours AFTER** RT
Faghihi (2024) [1]	Heckel-HT3000 (Fever-range WBH, wIRA)	Core Temp: 37.5°C – 41.5°C	3 to 4 hours	3-4 sessions (1-2x/week)	Administered **5–15 minutes BEFORE** RT
Ariyafar (2019) [3]	Celsius TCS (13.56 MHz Local Capacitive)	Max tolerable (Output-limiting)	60 minutes	Matches RT schedule	Administered up to **2 hours AFTER** RT

While the radio-oncological protocol (30 Gy in 10 fractions) was strictly homogeneous, the thermodosimetric execution revealed two distinct biophysical strategies. Local capacitive hyperthermia [2, 3] was sequenced sequentially *after* radiotherapy to maximize local synergistic DNA-repair inhibition, whereas whole-body hyperthermia [1] was applied immediately *before* radiotherapy (5–15 minute interval) to exploit maximum systemic vasodilation and tumor re-oxygenation during the radiation delivery.

3.2. Efficacy on Pain Management: Complete Response (CR) Rates

The primary efficacy endpoint evaluated was the Complete Response (CR) rate, strictly defined as a reduction of the BPI pain score to zero without an increase in analgesic intake. The combined administration of hyperthermia and radiotherapy demonstrated a profound and statistically significant superiority over standard monotherapy[1,2].

Within the experimental arms (RT+HT), 28 out of 71 patients achieved total pain elimination, translating to a pooled CR rate of **39.4%**. In stark contrast, only 3 out of 47 patients in the control arms (RT alone) achieved a BPI score of zero, yielding a drastically lower CR rate of **6.4%** [1,2,3].

Meta-analytical synthesis of the two Phase 3 RCTs utilizing the Mantel-Haenszel method revealed a massive treatment effect. The addition of non-invasive hyperthermia generated a highly significant Odds Ratio (OR) of **10.20** (95% CI: 2.76 - 37.69) favoring the experimental arm (**Figure 1**)[1,2]. Clinically, this indicates that the odds of a patient achieving complete pain relief are more than ten times higher when thermal radiosensitization is integrated into the protocol. Crucially, the statistical analysis revealed a complete absence of heterogeneity between the controlled trials ($I^2 = 0.0\%$, $p = 0.61$). This zero-heterogeneity metric mathematically validates that the 30 Gy + HT protocol generates an extremely robust and reproducible treatment effect across different oncology centers.[1,2]

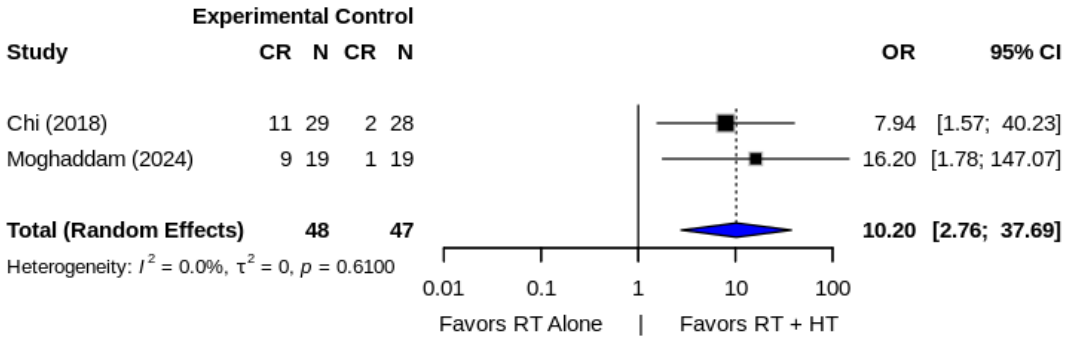


Figure 1. Forest plot for Complete Response (CR) rates. The plot illustrates the pooled Odds Ratio (OR) comparing standard radiotherapy plus hyperthermia (RT+HT) versus radiotherapy alone (RT). The blue diamond represents the overall pooled effect (OR = 10.20, 95% CI: 2.76 - 37.69), demonstrating a highly significant advantage for the combined RT+HT intervention. The complete absence of statistical heterogeneity ($I^2 = 0.0\%$, $p = 0.61$) indicates absolute consistency across the included trials.

3.3. Overall Clinical Benefit and Palliation Dynamics

Beyond absolute pain elimination, the overall objective clinical benefit—encompassing both Complete Responses and Partial Responses (PR)—was remarkably high. The Phase 2 prospective trial by Ariyafar et al. strongly corroborated the RCT findings, reporting that **78%** of the patients (18 out of 23) achieved an objective response (CR or PR) at 3 months post-treatment. This clinical success directly translated to a systemic reduction in drug dependency, with the number of patients requiring pain relief medications dropping significantly from 74% at baseline to 48% at 3 months. [3]

Furthermore, the integration of hyperthermia drastically altered the temporal dynamics of palliation, accelerating the onset of relief and extending its duration:

- **Time to Palliation:** Faghihi Moghaddam et al. observed rapid symptomatic improvement, noting that the time to achieve complete pain relief was as short as 10 days for patients undergoing systemic WBH. In contrast, the RT-alone cohort failed to reach this complete palliation endpoint during the equivalent follow-up period[1].
- **Duration of Response:** Chi et al. documented a profoundly extended duration of pain control. The median time to pain progression was significantly prolonged in the combined RT+HT group, a threshold that was not reached during the 24-week follow-up period. Conversely, complete responders in the RT-alone arm experienced pain progression at a median of only 55 days post-treatment[2].

3.4. Objective Radiological Response and Bone Ossification

A fundamental differentiator of the combined modality is its capacity to induce structural healing, shifting the paradigm from mere neuromodulation to objective tumor destruction. Radiological assessments confirmed that pain relief was closely correlated with structural bone stabilization[1,2].

- In the trial conducted by Chi et al., measurable radiologic lesions assessed via CT at week 12 demonstrated a significantly higher overall radiologic response rate in the RT+HT group compared to the control group (73.4% vs. 25.0%, $p = 0.014$). Furthermore, structural bone re-ossification of osteolytic lesions was observed in **53.3%** of the hyperthermia patients, compared to a mere 16.7% in the RT-alone cohort. [2]
- Similarly, Faghihi Moghaddam et al. utilized Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) to accurately monitor tumor cellularity. At the two-month follow-up, the mean tumor size in the RT+WBH group dropped by 11% (from 31.67 mm to 28.00 mm), whereas the RT-alone group showed a minimal reduction of only 6% (58.00 mm to 54.50 mm). [1]

3.5. Impact on Quality of Life (QoL) and Toxicity Profile

Pain relief functionally translated into an improved daily living experience. Quality of life metrics, assessed systematically via the EORTC QLQ-C30 questionnaire, mirrored the objective improvements in pain control [2, 3]. Patients in the RT+HT arms reported marked, statistically significant improvements in physical, role, cognitive, emotional, and social functioning scales [2, 3].

From a safety perspective, the quantitative analysis confirmed that the addition of oncological hyperthermia is an exceptionally safe adjuvant [1, 2, 3]. Crucially, the intervention did not produce any grade 3 or 4 severe adverse events in any of the analyzed cohorts [1, 2, 3]. By strictly quantifying thermal-related toxicities, the data reveals that adverse events were purely mild and transient. In the systemic WBH cohort, hyperthermia-related side effects were limited to transient skin erythema of the lower limb in 6.6% of patients and mild nausea in 3.3%, resolving spontaneously [1]. In the deep local hyperthermia cohort utilizing the Thermotron RF-8, local heating pain was reported in 48.3% of sessions (managed by immediate output de-escalation), while transient core body temperature elevations (>38°C) occurred in 20.6% of patients [2]. Additionally, localized subcutaneous fat induration persisted for several weeks exclusively in a specific subset of obese patients (13.7%) [2]. Overall, common radiation-induced gastrointestinal toxicities remained entirely unaffected by the integration of heat, confirming the excellent tolerability of thermoradiotherapy [1, 2].

4. DISCUSSION

4.1. Principal Findings

This meta-analysis highlights the substantial clinical benefit of integrating non-invasive oncological hyperthermia with standard palliative radiotherapy for the management of painful bony metastases. The quantitative synthesis demonstrates a profound superiority of the combined treatment modality (RT+HT) over radiotherapy alone, increasing the complete response rate from 6.4% to 39.4% [1, 2]. Furthermore, the combined treatment significantly accelerated the onset of pain relief and extended the duration of palliation, with the median time to pain progression not being reached during the designated follow-up periods in the controlled trials [1, 2].

4.2. Biological Mechanisms of Thermal Radiosensitization

The robust clinical outcomes observed can be attributed to the well-documented pleiotropic effects of hyperthermia on the tumor microenvironment [7]. Bony metastatic lesions often exhibit pronounced hypoxia and poor vascular penetration, rendering them inherently resistant

to standard radiation doses [9]. Both fever-range whole-body hyperthermia (WBH) and deep local hyperthermia induce localized vasodilation, thereby increasing tumor vascular perfusion and reducing tissue hypoxia [9]. This re-oxygenation acts as a highly potent radiosensitizer [7, 9]. Additionally, thermal stress directly inhibits the homologous recombination repair of RT-induced DNA damage in a time and temperature-dependent manner, ensuring superior rates of tumor cell apoptosis [8].

Specifically for osseous lesions, hyperthermia provides a unique biophysical advantage. Bone tissue is characterized by low thermal conductivity and low permeability compared with muscle [11]. Due to the difference in the dielectric constant, bones absorb more heat than surrounding soft tissues, and the marrow cavity absorbs even more heat due to its high fat content [11]. This allows for a selective thermal targeting of the metastatic site, maximizing the cytotoxic effect exactly where it is most needed.

4.3. Immunomodulation and Osteogenesis

Beyond direct cytotoxicity, hyperthermia serves as an essential immunological stimulant [14]. Heat shock stimulates tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) to mediate apoptosis, an effect that persists long after the active heating session has ended [12]. Furthermore, hyperthermia induces the aggregation of c-FLIP, a crucial regulator of apoptosis induced by death receptors [13]. Thermally enhanced immune effector cells, such as dendritic cells and natural killer cells, are generated systemically and migrate to the tumor site for proliferation and active killing, providing a powerful adjunctive immunotherapeutic effect [14].

Clinically, this cellular destruction is coupled with structural repair. Heat actively stimulates the function of osteoblastic cells to improve osteogenesis and decrease fracture risk [10]. This biological mechanism flawlessly explains the significant radiological re-ossification and bone density improvements documented in the interventional cohorts [2, 10].

4.4. The Dichotomy of Thermal Modalities: Local vs. Systemic Effects

A critical observation emerging from this meta-analysis is the nuanced difference in clinical outcomes based on the thermal delivery modality. Deep regional hyperthermia yielded a profoundly higher objective radiological response (73.4%) and structural re-ossification (53.3%) [2]. This is likely driven by the high thermal doses concentrated at the tumor site, which trigger Immunogenic Cell Death (ICD) [14]. The localized thermal stress induces the release of Heat Shock Proteins (HSP) and TRAIL, which act as endogenous danger signals, recruiting dendritic cells and Natural Killer (NK) cells to actively destroy the targeted lesion [12, 14].

Conversely, fever-range Whole-Body Hyperthermia (WBH) excelled in accelerating the palliation timeline, achieving complete pain relief in as little as 10 days [1]. While the direct radiological tumor shrinkage was more modest (11%) [1], the systemic elevation of core temperature (37.5-

41.5°C) generates massive systemic vasodilation [9]. This rapidly reduces tumor interstitial fluid pressure and modulates the excitability of pain-sensing nerves, providing a profound and immediate systemic analgesic effect [9]. This dichotomy suggests that the choice of thermal intervention should be tailored to the primary clinical objective: structural tumor control via ICD (Local HT) versus rapid, widespread systemic analgesia (WBH).

4.5. Impact on Quality of Life

Pain relief is intrinsically linked to functional independence. The administration of hyperthermia resulted in statistically significant improvements across multiple domains of the EORTC QLQ-C30 questionnaire, efficiently reversing decreased physical ability, fatigue, and loss of cognition, emotion, and social activity[2,3]. The integration of advanced thermal delivery systems—whether through deep regional RF capacitive heating or systemic WBH wIRA—proved highly safe [1,2,3]. As detailed in the safety analysis, treatment-related side effects were strictly quantified as mild and transient, and the addition of thermal stress did not exacerbate grade 3 or 4 severe adverse events [1, 2, 3]

4.6. Limitations and Future Directions

The primary limitation of this analysis is the relatively small number of available Phase 3 randomized controlled trials specifically isolating non-invasive hyperthermia in the palliative treatment of bony metastases [1, 2]. The inclusion of a Phase 2 single-arm trial limits the direct comparative statistical power, although its results robustly corroborate the response rates observed in the RCTs [3].

Furthermore, the included trials were statistically powered for local symptom control and palliation dynamics, featuring short-to-medium follow-up periods suitable for these primary endpoints (e.g., 3 to 6 months) [1, 2, 3]. Consequently, data regarding long-term Overall Survival (OS) or systemic Progression-Free Survival (PFS) were not systematically reported, reflecting the strictly palliative intent of the patient cohorts [1, 2, 3]. While the dramatic improvement in pain control and local structural re-ossification is undeniable [1, 2], future large-scale, multi-center trials should incorporate OS as a secondary endpoint to determine whether this profound local tumor control translates into a systemic survival advantage. Standardizing thermal dosimetry protocols across such trials will be essential to fully validate these highly promising palliative and immunological outcomes

4.7. Real-World Evidence and Expert Consensus

To bridge the gap between highly controlled randomized trials and routine clinical practice, it is crucial to evaluate real-world evidence and expert consensus. A recent retrospective analysis by Kim et al. (2024) [15] evaluated the integration of modulated electro-hyperthermia (mEHT) with palliative radiotherapy specifically in patients with pelvic and spinal bone metastases. Although its retrospective design precluded inclusion in our primary quantitative synthesis (to strictly preserve Level 1A statistical purity), the clinical outcomes robustly corroborate our meta-analytical findings. Kim et al. demonstrated that the RT+HT cohort achieved significantly superior pain reduction and a more prolonged duration of palliation compared to RT alone, confirming that the synergistic effects observed in our RCTs seamlessly translate into daily oncological workflows [15].

Furthermore, this clinical translation is strongly endorsed by independent radio-oncological experts. In a dedicated clinical commentary, Ghadjar et al. (2018) [16] validated the addition of local capacitive hyperthermia to standard palliative RT regimens for painful bone metastases. The consensus underscores that thermotherapy effectively counteracts the inherent clinical radioresistance of metastatic bone lesions by simultaneously disrupting cellular DNA repair mechanisms and enhancing targeted tumor oxygenation via increased perfusion [16]. These independent expert endorsements and real-world clinical observations reinforce both the biophysical rationale and the pressing clinical necessity of integrating thermoradiotherapy for optimal, long-term pain management.

5. Conclusions

This systematic review and meta-analysis provides robust Level 1A evidence (Oxford CEBM) demonstrating that non-invasive oncological hyperthermia acts as a potent, safe, and highly reproducible radiosensitizer and immunomodulator [1, 2, 3]. Supported by a moderate-to-high GRADE certainty—driven by a massive treatment effect that mathematically overcomes sample size limitations—the RT+HT combination categorically exceeds the palliative limits of standard radiotherapy alone. By increasing the odds of complete pain relief more than tenfold without exacerbating systemic toxicity, the thermoradiotherapy paradigm should be firmly integrated as a primary therapeutic approach in the modern management of painful bony metastases [1, 2, 3].

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