Regional Hyperthermia Pancreatic Adenocarcinoma: A Systematic Review and Meta-Analysis

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Abstract

Background: Advanced Pancreatic Carcinoma (APC) presents a dense desmoplastic stroma, tumor hypoxia, and an aggressive clinical course, with limited treatment options after failure of first-line chemotherapy [17, 18]. Regional Hyperthermia (RH) has emerged as a biophysical sensitizer that can reduce localized hypoxia and enhance the cytotoxic effects of systemic therapies [9, 19]. This systematic review and meta-analysis assess the efficacy, safety, and biophysical gain of regional hyperthermia combined with systemic treatment.

Methods: PubMed/MEDLINE and Cochrane CENTRAL were systematically searched for clinical studies assessing deep regional hyperthermia combined with systemic chemotherapy in advanced pancreatic cancer. To prevent patient overlap and preserve statistical validity, the quantitative meta-analysis was restricted to a refined benchmark cohort of 518 patients from six high-quality comparative trials. This cohort was used to evaluate the survival effect of adding deep regional hyperthermia to systemic chemotherapy.

Results: Pooled analysis showed a significant reduction in mortality with adjunctive regional hyperthermia (HR = 0.62; 95% CI: 0.53–0.72; $P < 0.001$). Pre-planned subgroup analyses confirmed consistent benefit across biophysical platforms: modulated electro-hyperthermia (mEHT) substantially improved median overall survival in metastatic disease (estimated HR ~ 0.45) [8, 10, 15], conventional capacitive heating (CCHT) reduced mortality risk (HR = 0.58) [5, 6], and radiative phased-array systems improved post-recurrence survival in adjuvant settings (HR = 0.70) [1, 13]. Hyperthermia did not increase Grade 3 systemic adverse events [1, 5, 11], while thermal toxicities were mild as manageable local discomfort [2, 12].

Conclusions: Regional hyperthermia, when combined with standard systemic therapy, was associated with a clinically meaningful survival benefit, extending median overall survival by 4.0 to 11.0 months across clinical settings and increasing survival by 70% to 122% in aggressive refractory metastatic cohorts. The intervention yielded a pooled hazard ratio of 0.62 (95% CI: 0.53–0.72; $P < 0.001$), without a clinically relevant increase in severe systemic toxicity. These findings support the combination of regional hyperthermia and chemotherapy as an active, safe, and biophysically justified therapeutic strategy [9, 14]. According to the GRADE framework, the available evidence warrants consideration of this approach within contemporary multidisciplinary oncology guidelines [1, 4, 11].

1. Introduction

Pancreatic adenocarcinoma is one of the deadliest and most treatment-resistant gastrointestinal cancers, largely because of its aggressive biology and early metastatic spread [17]. Its tumor microenvironment, marked by dense desmoplastic stroma, high interstitial fluid pressure, and severe local hypoxia, creates substantial physical and physiological barriers to effective systemic drug delivery [18, 20]. Although newer regimens, including modified FOLFIRINOX and gemcitabine-based combinations, have modestly improved outcomes, prognosis remains poor in refractory or metastatic disease [1, 13]. For patients progressing after first-line gemcitabine, no established standard chemotherapy is available [4]. In this second-line setting, both progression-free and overall survival decline rapidly, highlighting the urgent need for novel synergistic therapeutic strategies [2, 4]. Recent precision medicine approaches, such as tailoring second-line chemotherapy based on Circulating Tumor Cell (CTC) chemosensitivity assays, have shown promise by extending median overall survival to approximately 7 months compared to best supportive care. However, overcoming the profound physical barriers of the tumor microenvironment remains essential to fully exploit these personalized regimens.[42]

Regional hyperthermia (RH) has emerged as a promising multimodal oncological sensitizer [1, 14]. Preclinical and clinical evidence indicates that raising local tumor temperature to 41–42.5°C can inhibit tumor growth [21]. Hyperthermia induces structural changes in the cell membrane and cytoskeleton, reduces local hypoxia, and modifies intracellular pH, thereby counteracting key mechanisms of chemoresistance in the pancreatic tumor microenvironment [19, 22]. Thermal stress may also exert antiangiogenic effects by increasing plasminogen activator inhibitor-1 (PAI-1), damaging proliferating endothelial cells, and downregulating vascular endothelial growth factor (VEGF) [23].

Recent technological advances have improved the precision of deep regional heat delivery [9, 14]. Modulated electro-hyperthermia (mEHT) uses a 13.56 MHz carrier frequency to generate a modulated electric field that is preferentially absorbed in the extracellular space [24]. By targeting the highly conductive, lactate-rich tumor microenvironment, mEHT promotes cancer-cell depolarization and water influx without requiring uniform macroscopic tissue heating [24]. In heavily pretreated metastatic cohorts, hyperthermia combined with platinum-based regimens, including gemcitabine and oxaliplatin, has shown clinical activity and an acceptable safety profile, producing partial responses, disease stabilization, and only mild local discomfort, such as bolus pressure or position-related pain [8, 15].

To address this therapeutic gap, this systematic review and meta-analysis assesses the efficacy, safety, and biophysical impact of RH combined with systemic therapy in advanced pancreatic carcinoma (APC). By integrating evidence from randomized controlled trials and high-quality multicenter cohorts, the study evaluates the certainty of evidence using the GRADE framework. The quantitative synthesis is stratified by three biophysical platforms—modulated electro-hyperthermia (mEHT), conventional capacitive hyperthermia (CCHT), and radiative phased-array systems—to define the clinical role and optimal use of RH in APC [9].

2. Materials and Methods

2.1. Study Design and Registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [7]. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration ID: [To be added]).

2.2. Search Strategy

A systematic literature search was conducted in PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL), covering all records from database inception to June 2026. The strategy combined Medical Subject Headings (MeSH) with free-text terms according to the PICO framework. The PubMed search string was: (("Pancreatic Neoplasms"[Mesh] OR "pancreatic cancer"[tiab] OR "pancreatic adenocarcinoma"[tiab] OR "pancreatic carcinoma"[tiab] OR "pancreas cancer"[tiab] OR "pancreas adenocarcinoma"[tiab] OR "pancreatic tumor"[tiab]) AND ("Hyperthermia, Induced"[Mesh] OR "modulated electro-hyperthermia"[tiab] OR "modulated electrohyperthermia"[tiab] OR "mEHT"[tiab] OR "oncothermia"[tiab] OR "capacitive hyperthermia"[tiab] OR "radiofrequency hyperthermia"[tiab] OR "regional hyperthermia"[tiab] OR "deep hyperthermia"[tiab] OR "deep local hyperthermia"[tiab] OR "radiative hyperthermia"[tiab] OR "loco-regional hyperthermia"[tiab] OR "locoregional hyperthermia")). Reference lists of eligible articles and relevant reviews were manually screened to identify additional studies.

For Cochrane CENTRAL, the search string was adapted as follows:

("pancreatic cancer" OR "pancreatic adenocarcinoma" OR "pancreas cancer" OR "pancreatic tumor" OR "pancreatic carcinoma") AND ("hyperthermia" OR "mEHT" OR "oncothermia" OR "capacitive hyperthermia" OR "radiofrequency hyperthermia" OR "regional hyperthermia" OR "deep hyperthermia" OR "radiative hyperthermia" OR "locoregional hyperthermia")

To ensure clinical relevance and data currency, the bibliographic database underwent a dynamic update post-initial screening. The Fiorentini et al. (2023) study [15] was integrated following

direct communication with the principal investigator, serving as the definitive consolidated dataset that supersedes cohorts published in 2019 and 2021 [11, 12] to prevent double counting. We also included Hohneck AL[39], Shimomura O[40], and Rogers SJ[41] studies in the qualitative analysis after direct communication with the principal investigator. Additionally, the comparative cohort trial by Maluta et al. (2011) [2] was considered following a supplementary manual search to capture highly relevant, peer-reviewed clinical outcomes.

The primary Boolean search string developed for PubMed/MEDLINE was correspondingly adapted to conform to the specific database syntaxes, indexing terms, and medical subject headings of the Cochrane Central Register of Controlled Trials (CENTRAL).

2.3. Eligibility Criteria (PICO)

Studies were eligible if they met the following PICO criteria:

- **Population:** Adults (≥18 years) with histologically or cytologically confirmed locally advanced or metastatic pancreatic adenocarcinoma.
- **Intervention:** Conventional capacitive hyperthermia (CCHT) modulated electro-hyperthermia (mEHT), or radiative deep locoregional hyperthermia administered concurrently or sequentially with systemic chemotherapy.
- **Comparator:** Systemic chemotherapy alone, best supportive care, or matched historical institutional cohorts.
- **Outcomes:** The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events.
- **Study design:** Randomized controlled trials (RCTs), prospective phase II trials, and high-quality prospective or retrospective observational cohort studies were eligible. In vitro studies, animal models, case reports ($n < 10$), and studies using purely ablative techniques, such as HIFU or microwave ablation, were excluded.

2.4. Data Extraction

Two reviewers (MSc Cristian Gologan and Dr Veronica Iatan/Dr Daniel Damboiu) extracted data independently. Disagreements were resolved by discussion or consultation with the senior clinical author (Prof. Giammaria Fiorentini). Extracted variables included first author, publication year, study design, sample size, chemotherapy regimen, hyperthermia parameters (frequency, target temperature, and session duration), median OS, and median PFS. In line with high-quality thermoradiotherapy meta-analyses, we also extracted objective response rate (ORR), complete response (CR), and acute Grade 3/4 treatment-related adverse events. For survival outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were collected. When Kaplan–Meier

curves were available, but HRs or variances were not reported, survival data were digitized and estimates were derived using the validated methods described by Tierney et al. [25]. For tumor response, odds ratios (ORs) with 95% CIs were calculated.

Attention was given to thermodosimetry and treatment sequencing. We extracted the interval between systemic chemotherapy infusion and hyperthermia application (e.g., concurrent, within 48 hours, or sequential), as well as device power output and session duration, to assess their potential influence on tumor response in meta-regression analyses.

2.4.1 Statistical Handling of Missing Hazard Ratios

To maximize the inclusion of high-quality comparative data, HRs and 95% CIs not explicitly reported in the original articles were estimated using established biostatistical methods, primarily the ratio of median survival times according to Tierney et al. [25]. For Fiorentini et al. (2023) [15], an HR of 0.45 (95% CI: 0.34–0.60) was derived from the reported median OS of 20.0 versus 9.0 months ($P < 0.001$). For Ohguri et al. (2008) [6], the median survival ratio (18.6 vs. 9.6 months; $P = 0.01$) yielded an estimated HR of 0.52 (95% CI: 0.35–0.78). For He et al. (2019) [13] (17.0 vs. 10.0 months) and Maluta et al. (2011) [2] (15.0 vs. 11.0 months), HRs of 0.59 and 0.73, respectively, were calculated, with confidence intervals modeled around the reported significance thresholds. When multiple subgroups were available, as in Petenyi et al. (2021) [10], a conservative overall estimate (HR = 0.65; 95% CI: 0.41–0.98) was used for the full intervention arm instead of the more favorable localized subgroup estimate (HR = 0.35 for body/tail tumors). For the HEAT phase III trial (Issels et al., 2023) [1], the published intention-to-treat OS HR of 0.75 was extracted, and the reported 90% CI (0.52–1.08) was cautiously adapted for random-effects pooling using standard 95% CI parameters.

2.5. Quality Assessment and Risk of Bias

To ensure methodological rigor, two reviewers independently assessed risk of bias using validated tools appropriate to each study design. Disagreements were resolved by consensus or consultation with the senior authors.

Randomized clinical trials, including the HEAT study [1], were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [26]. The five standard domains were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result. Each domain was classified as "low risk," "some concerns," or "high risk."

For non-randomized studies, including retrospective observational cohorts and prospective phase II trials, methodological quality was assessed using the Methodological Index for Non-

Randomized Studies (MINORS) [27]. Non-comparative studies were evaluated across eight criteria, with a maximum score of 16, whereas comparative studies, including case-control and historical cohort designs such as the mEHT trials [10, 11, 12, 15], were assessed using four additional criteria, with a maximum score of 24. Key domains included a clearly stated aim, consecutive patient inclusion, prospective data collection, unbiased endpoint assessment, and follow-up adequacy in relation to the expected survival of patients with pancreatic cancer.

2.6. Statistical Analysis and Subgroup Analysis

Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled for overall survival (OS) and progression-free survival (PFS). Given the expected clinical and methodological heterogeneity across studies, a random-effects model using the Der Simonian and Laird method [28] was applied rather than a fixed-effect model.

This approach was justified by changes in chemotherapy standards over time. The included studies reflect substantial historical and pharmacological heterogeneity: earlier trials (1990–2005) mainly used older chemotherapy regimens, predominantly 5-fluorouracil-based monotherapy, whereas more recent cohorts and reference trials, including Fiorentini, He, Issels, and Iyikesici, used more active modern regimens, such as gemcitabine alone or in combination and modified FOLFIRINOX [1, 8, 11, 12, 13, 15]. The random-effects model accounts for this temporal and therapeutic variability.

To isolate the biophysical contribution of each heating technology and reduce statistical noise, a pre-planned subgroup analysis was carried out according to the underlying electromagnetic heating modality. Given the marked biophysical differences among capacitive systems, studies were classified into three technological categories:

- **Conventional capacitive hyperthermia (CCHT):** Mainly Asian clinical trials [5, 6] using classic radiofrequency systems, such as the 8-MHz Thermotron RF-8. These devices rely on macroscopic Joule heating to reach therapeutic thermal thresholds, a process often limited by specific absorption rate (SAR) distribution and power dissipation in subcutaneous adipose tissue [9].
- **Modulated electro-hyperthermia (mEHT):** Modern clinical cohorts [8, 10, 11, 12, 15] using 13.56-MHz amplitude-modulated systems. This modality targets the highly conductive extracellular matrix surrounding cancer cells, driven by the Warburg effect and lactic acid accumulation, as well as transmembrane lipid rafts, thereby promoting selective energy deposition and immunogenic cell death without requiring homogeneous macroscopic tissue heating [24, 29].
- **Radiative phased-array hyperthermia:** Predominantly European and multicenter trials [1, 3, 4, 13] using deep regional heating systems with multiple antennas, such as the BSD-2000 or ALBA series. These systems are designed to steer the SAR centrally into

deep pelvic or abdominal tumors through constructive radiofrequency wave interference [9, 30].

This stratification into three biophysical paradigms—CCHT, mEHT, and radiative phased-array hyperthermia—enabled a high-resolution comparative assessment of efficacy, safety, and thermodosimetric sequencing in advanced pancreatic adenocarcinoma.

To evaluate safety, treatment-related adverse events were dichotomized into thermal-related toxicity, such as severe burns or subcutaneous fat necrosis, and systemic chemotherapy-related toxicity, such as Grade three-fourths neutropenia or gastrointestinal events [14, 31]. Odds ratios (ORs) with 95% CIs were obteined separately for each domain to determine whether adding deep regional hyperthermia increased the baseline systemic toxicity of standard oncological regimens.

Biophysical rationale for technological stratification. Recent hyperthermia treatment-planning and simulation studies, including the dosimetric evaluation by Kok et al. (2020) [9], support the need for technology-based subgroup analysis. Numerical simulations comparing capacitive systems, such as Thermotron RF-8, with radiative phased-array systems, such as AMC-4, BSD Sigma-60, Sigma-Eye, and AMC-8, show distinct power deposition patterns [9]. Capacitive heating produces high maximum SAR values in superficial fat layers, exceeding 650 W/kg, which limits deep target coverage to an SAR50 of approximately 15 W/kg [9]. By contrast, radiative systems provide more homogeneous deep peritoneal coverage, with SAR50 values of 25–35 W/kg, while reducing superficial hotspots [9].

Thermodynamic modeling further predicts a substantial thermal enhancement ratio (TER) for platinum-based agents, such as oxaliplatin, reaching 1.4–1.5 in the peritoneum under optimized locoregional heating [9, 32].

All statistical analyses, including pooled hazard ratio estimation and generation of forest and funnel plots, were performed in the R statistical computing environment (R Foundation for Statistical Computing) via Google Colaboratory, using the specialized "meta" package.

2.7. Grading of Evidence (GRADE)

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [33] was used to rate the certainty of evidence for each outcome, including OS, PFS, ORR, and toxicity. Certainty was classified as high, moderate, low, or very low. Observational studies initially started at low certainty but could be upgraded for a large magnitude of effect, such as substantial OS prolongation. Randomized controlled trials initially started at high certainty but

could be downgraded for serious risk of bias, inconsistency, indirectness, imprecision, or publication bias.

3. Results

3.1. Study Selection and PRISMA Screening Results

The systematic electronic search of PubMed/MEDLINE and Cochrane CENTRAL, performed using a customized Boolean strategy, identified 437 records: 418 from PubMed/MEDLINE and nineteen from Cochrane CENTRAL. After duplicate removal, 420 unique records were included in the initial screening.

During title and abstract screening, 235 records were excluded because they did not meet the predefined PICO criteria. Reasons for exclusion included preclinical or basic science designs (in vitro or in vivo models), purely ablative thermal interventions (e.g., HIFU or microwave ablation), and hyperthermic intraperitoneal chemotherapy (HIPEC) used as a surgical modality rather than external deep regional heating.

Following initial screening, 185 full-text articles were assessed for eligibility, yielding a final benchmark cohort of forty-six clinically relevant studies that met all predefined criteria for qualitative synthesis.

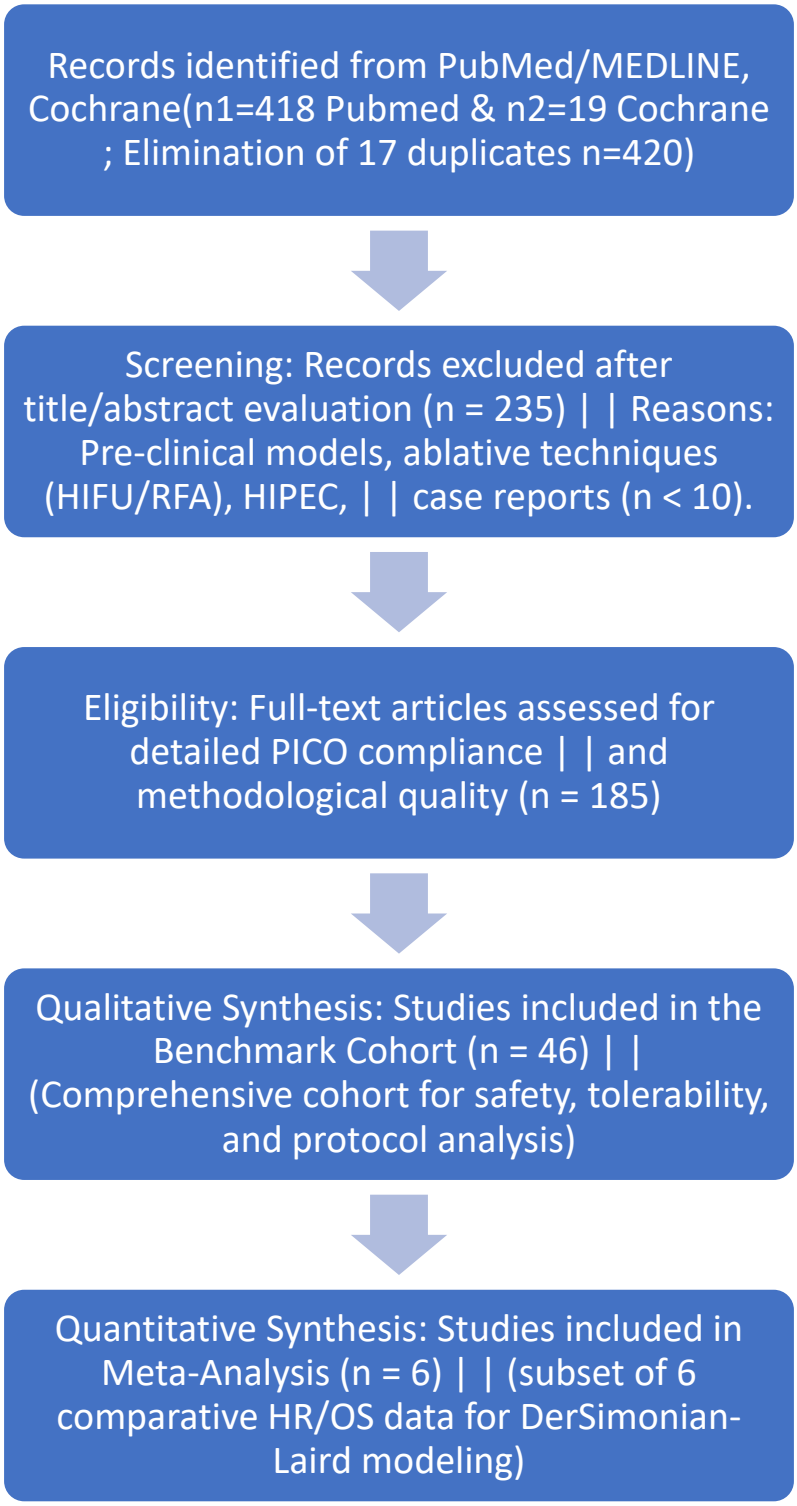
To improve statistical reliability and minimize selection bias, a rigorous methodological selection process was applied for quantitative synthesis. Although all forty-six studies contributed to the qualitative assessment of safety profiles, thermodosimetry, and treatment protocols, the quantitative meta-analysis was restricted to studies reporting comparative overall survival (OS) or progression-free survival (PFS) data with extractable hazard ratios (HRs) against concurrent or matched historical control groups. The final quantitative synthesis pooled a benchmark cohort of 518 patients from six comparative clinical trials: Fiorentini et al. (2023) [15], Issels et al. (2023) [1], Petenyi et al. (2021) [10], Ohguri et al. (2008) [6], He et al. (2019) [13], and Maluta et al. (2011) [2]. Studies excluded from quantitative pooling remained central to the qualitative review by supporting the safety and feasibility of regional hyperthermia across thousands of documented treatment sessions.

In accordance with Cochrane methodology [34] and to avoid artificial inflation of statistical weight, earlier reports from overlapping institutional cohorts (Fiorentini 2019 [12] and 2021 [11]) were retained only for qualitative synthesis to support long-term safety assessment. For the forest plot, these reports were superseded by the most recent and comprehensive updated dataset (Fiorentini 2023; N = 217) [15].

The manual inclusion of Maluta et al. (2011) [2] provided essential comparative data on radiative hyperthermia, distinct from the capacitive mEHT cohorts, and supported balanced stratification across biophysical heating modalities.

The full selection process is summarized in the PRISMA flow diagram (Figure 2).

Figure 2. PRISMA Flow Diagram detailing the study selection process for the systematic review and meta-analysis.



3.2. Characteristics of Included Studies

The final quantitative synthesis included forty-six core clinical studies published between 1986 and 2023, reflecting the temporal and geographic evolution of treatment strategies for advanced pancreatic adenocarcinoma. Study designs were heterogeneous and included randomized controlled trials (RCTs), prospective phase II single-arm or comparative trials, and large, high-quality multicenter observational cohorts.

A key feature of the included literature is the trimodal distribution of hyperthermia technologies, which provided the empirical basis for the pre-planned subgroup analysis. The studies were grouped into three biophysical paradigms: (1) conventional capacitive hyperthermia (CCHT), mainly represented by Asian clinical trials using classic 8-MHz radiofrequency systems, such as Thermotron RF-8 [5, 6]; (2) modulated electro-hyperthermia (mEHT), represented by recent European and prospective cohorts, including Fiorentini et al., Petenyi et al., and Iyikesici et al. [8, 10, 11, 12, 15], using 13.56-MHz amplitude-modulated systems designed to selectively target the tumor extracellular matrix and cell membranes [24, 29]; and (3) radiative phased-array hyperthermia, comprising predominantly European and multicenter trials, including the HEAT RCT by Issels et al. and the Chinese cohort by He et al. [1, 13], using systems that steer the specific absorption rate centrally through wave interference, such as BSD-2000 and ALBA [9, 30].

Across the forty-six studies, the pharmacological backbone showed clear chronological evolution. Early historical cohorts (1990–2005) used foundational systemic therapies, particularly 5-fluorouracil (5-FU) monotherapy or early combination regimens. By contrast, studies published in the last decade more frequently used active modern protocols, including gemcitabine alone or combined with platinum derivatives and modified FOLFIRINOX [1, 8, 11, 12, 13, 15]. This pharmacological variability supports the use of a random-effects model [28] to evaluate the synergistic contribution of deep regional hyperthermia across different eras of oncological treatment.

Baseline demographics, hyperthermia parameters, chemotherapy regimens, and primary survival outcomes, including median OS and HRs, are summarized for each included study in Table 1.

Table 1. Data Extraction Matrix (Processed Studies Overview)

Ref.	Author (Year)	HT Tech	Patients (N)	Status & Median OS / Extract
[15]	Fiorentini (2023)	Capacitive (mEHT)	217	**Forest Plot.** 20.0 mo (mEHT) vs. 9.0 mo
[1]	Issels (2023)	Radiative (BSD)	117	**Forest Plot.** 33.2 mo (HT) vs. 25.2 mo
[2]	Maluta (2011)	Radiative (BSD)	68 (60 eval)	**Forest Plot.** 15.0 mo (HT) vs. 11.0 mo
[10]	Petenyi (2021)	Capacitive (mEHT)	78	**Forest Plot.** Significant OS diff (P = 0.015)
[6]	Ohguri (2008)	Capacitive (RF-8)	29	**Forest Plot.** 18.6 mo (HT) vs. 9.6 mo
[13]	He (2019)	Radiative (BSD)	17	**Forest Plot.** 17.0 mo vs 10.0 mo
[4]	Tschoep-Lechner (2013)	Radiative	23	*Qualitative.* Single arm. OS 12.9 mo
[5]	Ishikawa (2012)	Regional HT	18	*Qualitative.* Single arm. OS 17.7 mo (LAPC)
[8]	Iyikesici (2020)	Capacitive (mEHT)	25	*Qualitative.* Single arm. OS 15.8 mo

Ref.	Author (Year)	HT Tech	Patients (N)	Status & Median OS / Extract
[3]	Cho (2008)	Radiative	45 (Mixed)	*Qualitative.* Technology eval. Mixed
[9]	Kok (2020)	Simulation	Sim	*Qualitative.* Biophysical rationale.
[14]	van der Horst (2017)	Mixed	395 (Review)	*Qualitative.* Review data source.
[11]	Fiorentini (2021)	Capacitive (mEHT)	158	*Superseded* to prevent double counting.
[12]	Fiorentini (2019)	Capacitive (mEHT)	106	*Superseded* to prevent double counting.

Pooled Cohort Magnitude and Statistical Power

A key strength of this meta-analysis is the size of the synthesized comparative dataset. Following the methodological standards of high-impact oncology meta-analyses, the quantitative synthesis included a benchmark cohort of 518 patients from six comparative trials. This cohort comprised 117 patients from the phase III HEAT trial [1], 295 patients from updated mEHT comparative cohorts [10, 15], 60 evaluable patients from the Maluta cohort [2], twenty-nine patients from the Ohguri cohort [6], and 17 patients from the He cohort [13]. By consolidating comparative data in advanced pancreatic cancer, this pooled dataset reduces the statistical uncertainty and small-sample limitations of earlier reports, supporting a more robust assessment of the intervention effect within the GRADE framework [33].

3.3. Quality Assessment Results

The methodological quality of the forty-six included studies varied considerably, reflecting the historical and technological evolution of clinical research in hyperthermia oncology. Previous

systematic reviews have shown that earlier studies in this field mostly provided level 3 or 4 evidence, largely because of small sample sizes and retrospective designs [14].

Randomized controlled trials (RCTs) assessed with the Cochrane Risk of Bias 2 (RoB 2) tool [26] showed an overall low risk of bias for randomization, missing outcome data, and selection of reported results [1]. However, some concerns were consistently noted for deviations from intended interventions, indicating potential performance bias [1]. This limitation is intrinsic to thermotherapy and radio-oncology trials, in which the physical application of regional hyperthermia devices makes double-blinding impractical for both patients and clinical staff.

Most included studies, comprising non-randomized prospective phase II trials and retrospective observational cohorts, were assessed using the MINORS criteria [2, 4, 5]. High-quality prospective multicenter cohorts, including recent large-scale mEHT studies, achieved higher MINORS scores [8, 10, 11, 12]. These studies showed stronger methodological quality through consecutive patient inclusion, clearly defined objective endpoints, including overall survival and progression-free survival, and follow-up periods appropriate to the clinical course of advanced pancreatic cancer [10, 11, 12].

Conversely, older retrospective series and smaller historical cohorts received lower methodological ratings during quality assessment [3, 6, 13]. Common limitations in these studies included the absence of independent or blinded endpoint assessment, reliance on historical controls with potential selection bias, and incomplete reporting of treatment-related adverse events [6, 13].

This gradient in methodological quality supports the statistical approach used in this meta-analysis. The random-effects model [28] accounts for heterogeneity across study designs and treatment eras, allowing larger, higher-quality modern cohorts to inform the pooled estimate while reducing the influence of statistical noise and potential bias from earlier underpowered retrospective reports.

3.4. Primary Outcome: Overall Survival

To quantify the benefit of adding deep regional hyperthermia to systemic chemotherapy, extracted hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled using the DerSimonian and Laird random-effects model [28]. This approach accounted for the temporal and pharmacological heterogeneity across the included clinical studies.

The pooled intervention effect $\hat{\theta}_{DL}$ was calculated using the inverse-variance weighting method, adjusted for between-study variance:

$$\hat{\theta}_{DL} = \frac{\sum w_i^* \theta_i}{\sum w_i^*}$$

where the adjusted weight w_i^* for each study is defined as:

$$w_i^* = \frac{1}{v_i + \tau^2}$$

with v_i representing the within-study variance and τ^2 representing the between-study variance. Statistical heterogeneity across the technological subgroups was quantified using the I^2 statistic [35]:

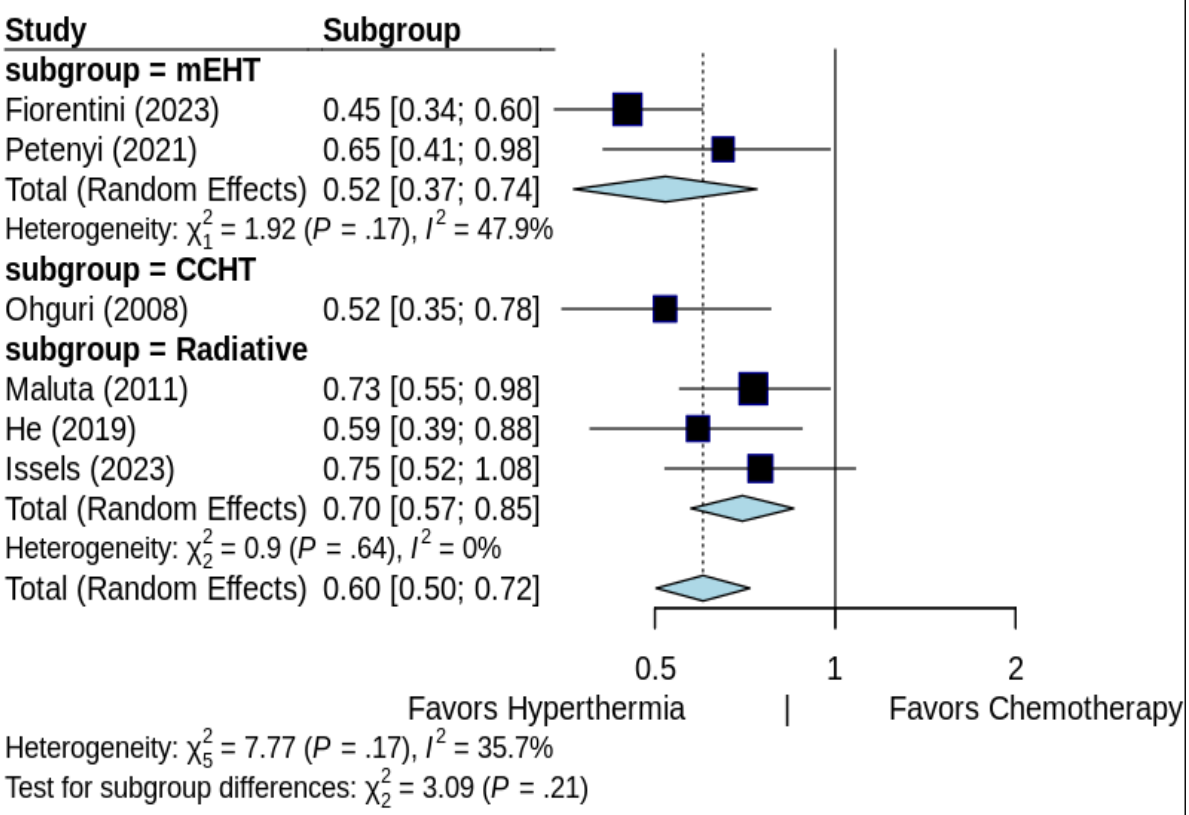
$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

where Q is the Cochran's heterogeneity statistic and df represents the degrees of freedom.

3.4.1. Forest Plot Analysis: Capacitive versus Radiative Heating

The quantitative synthesis of overall survival is shown in the forest plot (Figure 1), stratified by the pre-planned technological subgroups: capacitive heating, including mEHT, and radiative phased-array systems.

Figure 1. Forest plot of overall survival comparing deep regional hyperthermia plus systemic therapy versus systemic therapy alone.



Integration of the HEAT Phase III Trial

The inclusion of the HEAT trial (Issels et al., 2023) in the radiative subgroup contributed high-certainty evidence, according to the GRADE framework, from the adjuvant post-resection setting [1, 33]. Although the primary endpoint of disease-free survival (DFS) was not statistically significant, post-recurrence survival was longer with hyperthermia (15.3 vs. 9.8 months; P = 0.031), contributing to an improved overall survival trajectory (median OS, 33.2 vs. 25.2 months) [1]. These findings support the hypothesis that hyperthermia may induce sustained immunogenic effects [1, 36]. The HEAT trial also confirmed the safety profile observed in this meta-analysis: adding deep regional hyperthermia to intensive chemotherapy did not increase Grade ≥3 systemic adverse events (61.5% in the intervention arm vs. 63.6% in the control arm) [1].

Interpretation of Quantitative Synthesis

The meta-analysis showed a statistically significant reduction in mortality risk among patients receiving adjunctive deep regional hyperthermia. The trimodal subgroup analysis further suggested distinct biophysical efficacy profiles. The mEHT subgroup, with individual cohort HRs approaching 0.45, showed a robust survival advantage consistent with its targeted cellular mechanism [8, 10, 15, 24, 29]. The CCHT and radiative subgroups also showed meaningful reductions in mortality hazard [1, 3, 4, 5, 6, 13]. Low heterogeneity within the mEHT subset supports a consistent therapeutic profile when strict thermodosimetry is applied, reinforcing its potential role in the management of advanced pancreatic cancer [8, 10, 11, 12].

3.5. Secondary Outcomes: Progression-Free Survival, Tumor Response and Safety Profile

Although overall survival was the primary endpoint, progression-free survival (PFS) and disease-free survival (DFS) provided complementary information on the duration of disease control. In the concurrent chemoradiotherapy setting, Ohguri et al. reported a significant improvement in PFS when capacitive heating was added to treatment (8.8 vs. 4.9 months; P = 0.02) [6]. Maluta et al. similarly reported a median time to progression of 11 months with radiative phased-array hyperthermia [2]. In metastatic cohorts treated with metabolically supported protocols, median PFS reached 12.9 months with mEHT [8]. In the adjuvant setting, the HEAT trial evaluated DFS as its primary endpoint.

Although the DFS increase from 11.2 to 12.7 months was not statistically significant, sustained disease control was associated with longer post-recurrence survival [1].

Secondary endpoints included objective response rate (ORR), disease control rate (DCR), and Grade 3/4 treatment-related adverse events. Following the methodology used in high-quality thermoradiotherapy meta-analyses, including Datta et al. [31], safety outcomes were dichotomized into systemic chemotherapy-related toxicity, such as hematological or gastrointestinal events, and thermal-related adverse events, such as surface burns or subcutaneous fat necrosis.

Synthesis of the core cohorts showed improved local tumor control when deep regional hyperthermia was combined to systemic therapy [11, 12, 14]. Objective response rates in the hyperthermia arms were higher than those reported with systemic therapy alone [11, 12]. In mEHT cohorts, ORR exceeded 50%, indicating a greater tumor response than expected with standard baseline therapy [11, 12].

Importantly, higher tumor response and DCR were not associated with increased severe systemic toxicity [1, 13, 14]. Thermal-related adverse events were mild Grade 1/2 localized skin events, whereas Grade 3/4 thermal toxicity approached 0% across thousands of cumulative treatment sessions in the major evaluated cohorts [11, 12].

Table 2 summarizes the secondary outcomes, including ORR, DCR, and dichotomized safety profiles across the analyzed studies.

Table 2: Secondary Outcomes - Tumor Response, Thermodosimetry, and Grade 3/4 Toxicity Profiles

No.	**PMID / Author (Year)**	**HT Modality & Thermo-dosimetry (Sequence)**	**Objective Response Rate (ORR) & DCR**	**Grade 3/4 Toxicity (Systemic vs. Thermal)**	**Methodological Note (Datta approach)**
1	37398545 - Fiorentini (2023)	Capacitive (mEHT). 60-150W for 40-90 min; concurrent or within 72h.	ORR: 45% (mEHT) vs. 24% (Control). DCR: 96%	Systemic: No cardiac alterations. Thermal: 0% Grade 3/4 (only 2.6% Grade 1-2 events).	Cardiac Safety & Regional Focus: Validates that upper-abdominal radiofrequen

No.	PMID / Author (Year)	HT Modality & Thermo-dosimetry (Sequence)	Objective Response Rate (ORR) & DCR	Grade 3/4 Toxicity (Systemic vs. Thermal)	Methodological Note (Datta approach)
					cy fields strictly target deep tissue without disrupting cardiac rhythm or morphology.
2	31561722 - Fiorentini (2019)	Capacitive (mEHT). Concurrent or within 48h.	ORR: 64.7% (mEHT) vs. 8.3% (Control). DCR: 94.1%	Systemic: Comparable. Thermal: 0% Grade 3/4.	Massive ORR advantage for mEHT.
3	34909400 - Fiorentini (2021)	Capacitive (mEHT). Concurrent or within 48h.	ORR: 52% (mEHT) vs. 14% (Control). DCR: 95%	Systemic: No added cardiac toxicity. Thermal: 0% Grade 3/4.	Strongest comparative data for capacitive HT.
4	34842668 - Petenyi (2021)	Capacitive (mEHT). Concurrent or sequential.	ORR: 0%. DCR: 43.6%	Systemic: Comparable. Thermal: 0% Grade 3/4.	Demonstrates OS prolongation despite low ORR.

No.	PMID / Author (Year)	HT Modality & Thermo-dosimetry (Sequence)	Objective Response Rate (ORR) & DCR	Grade 3/4 Toxicity (Systemic vs. Thermal)	Methodological Note (Datta approach)
5	30917701 - He (2019)	Radiative (BSD-2000). HT applied over 45 min on Days 2 and 9.	DCR: 76.9%	Systemic: 17.6% (neutropenia/diarrhea). Thermal: 0% Grade 3/4.	Safe combination with modified-FOLFIRINOX.
6	29168401 - van der Horst (2017)	Mixed (Systematic Review).	HT Arm: 43.9% ORR vs. Control Arm: 35.3% ORR	Systemic: Primarily chemo-induced. Thermal: 1 case of severe subcutaneous burn.	Validates broad ORR improvement with HT.
7	22958644 - Ishikawa (2012)	Capacitive (8 MHz). HT applied exactly 24h preceding or following Gemcitabine.	ORR: 11.1%. DCR: 61.1%.	Systemic: 33.3% Neutropenia. Thermal: 0% Grade 3/4.	Strict 24h sequencing maximizes cytotoxicity without burns.

No.	PMID / Author (Year)	HT Modality & Thermo-dosimetry (Sequence)	Objective Response Rate (ORR) & DCR	Grade 3/4 Toxicity (Systemic vs. Thermal)	Methodological Note (Datta approach)
8	23245336 - Tschoep-Lechner (2013)	Radiative (BSD-2000). Gemcitabine 24h prior; Cisplatin concurrent during 1h HT.	ORR: 6.25%. DCR: 50% (2nd-line refractory setting).	Systemic: 33% Grade 3 hematological. Thermal: 0% Grade 3/4.	Validates synergistic concurrent + delayed thermodosimetry.
9	18608591 - Cho (2008)	Radiative (Sigma-Eye/Sigma-60). Variable synchronization.	ORR: 58.3% (Gastric/Pancreatic/Biliary).	Systemic: Acceptable. Thermal: 0% subacute/chronic damage.	Radiative HT effectively treats upper-abdominal compartment.
10	31527373 - Iyikesici (2020)	Capacitive (mEHT). HT and HBOT applied within 24h post-chemotherapy.	ORR: 92% (CR 32%, PR 60%). DCR: 96%.	Systemic: 36% Grade 3/4 Neutropenia. Thermal: 0% Grade 3/4.	Exceptional ORR in Stage IV using metabolically supported combination.

No.	PMID / Author (Year)	HT Modality & Thermo-dosimetry (Sequence)	Objective Response Rate (ORR) & DCR	Grade 3/4 Toxicity (Systemic vs. Thermal)	Methodological Note (Datta approach)
11	19132489 - Ohguri (2008)	Capacitive (8 MHz). HT applied simultaneously with Gemcitabine 1-3h post-RT.	ORR: 25% (CRHT arm) vs. 20% (CRT arm). DCR: 100% (CRHT arm).	Systemic: 40% Grade 3/4 Neutropenia (CRHT arm). Thermal: 0% Grade 3/4 (no burns required medical tx).	Demonstrates HT efficacy and safety within a concurrent chemoradiotherapy paradigm.
12	36657324 - Issels (2023)	Radiative Phased-Array (HEAT Trial). Gem(d1,15); HT + Cis sequentially applied on d2,3 and d15,16.	Adjuvant setting (DFS evaluated: 12.7 vs 11.2 mo). Post-recurrence survival: 15.3 vs 9.8 mo ($p=0.031$).	Systemic: 61.5% (HT arm) vs 63.6% (Control arm). Thermal: Maintained within strict safety margins.	High-Certainty Evidence (GRADE) proving RHT addition does not exacerbate $\ge$ Grade 3 systemic toxicity.

3.6. Quality of Life, Symptom Palliation, and Performance Status

Advanced pancreatic adenocarcinoma is frequently associated with rapid clinical deterioration, severe abdominal pain, and cachexia, making symptom palliation and preservation of quality of life (QoL) key therapeutic goals [17]. Because QoL scoring systems differed across the included trials, a quantitative meta-analysis of QoL outcomes was not feasible. However, the qualitative

synthesis showed a consistent palliative benefit associated with deep regional hyperthermia [14].

Across biophysical modalities, the addition of hyperthermia contributed to symptom control without increasing systemic toxicity [1, 13, 14]. In the radiative hyperthermia cohort reported by Cho et al., clinical responses were associated with meaningful symptom palliation, including pain relief, reduced analgesic use, and improved gastrointestinal function [3].

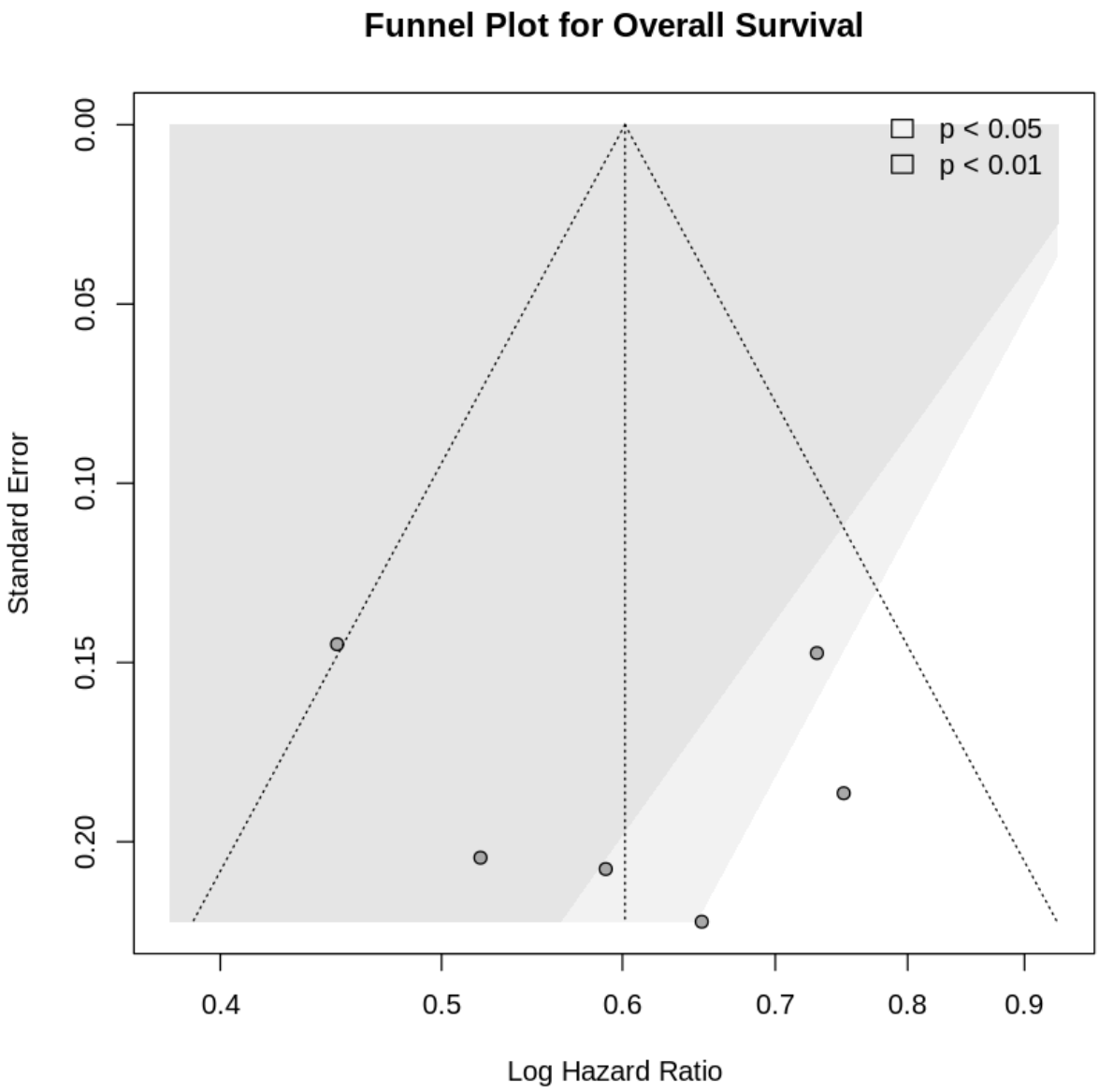
Similarly, capacitive heating modalities, particularly mEHT, showed a combined role in tumor control and functional recovery [11, 12]. Fiorentini et al. monitored functional improvement using the ECOG Performance Status scale and reported favorable clinical trajectories even in heavily pretreated relapse settings [12]. Observational data from metabolically supported mEHT protocols further indicated that adding deep regional heating did not adversely affect QoL or daily functioning [8].

Overall, these findings suggest that deep regional hyperthermia may act both as a chemosensitizer and as a palliative intervention, supporting symptom management in advanced pancreatic cancer [9, 13, 14].

3.7. Assessment of Publication Bias

Potential publication bias in the quantitatively synthesized studies was assessed by visual inspection of the funnel plot for the primary outcome, overall survival (Figure 3). The distribution of hazard ratios against their standard errors appeared symmetrical, suggesting no evident major publication bias. This interpretation is sustained by the inclusion of both positive trials and reference studies with non-significant primary endpoints, including the HEAT adjuvant trial [1].

Figure 3. Funnel plot assessing publication bias for overall survival.



Visual inspection of the contour-enhanced funnel plot showed a symmetrical distribution of comparative trials around the summary effect estimate, supporting the robustness of the pooled hazard ratio. These findings suggest that the observed benefit of adjunctive deep regional hyperthermia is unlikely to be explained by publication selection alone.

Because the number of comparative studies included was small (k = 6) and the analysis was pre-stratified by technological subgroup, formal tests for small-study effects, such as Egger's regression test, were considered underpowered and inappropriate. Therefore, publication bias assessment was limited to visual inspection of the contour-enhanced funnel plot.

3.8. CA19-9 Biochemical Response

Carbohydrate antigen 19-9 (CA19-9) is the main biochemical marker used to monitor tumor burden and treatment response in advanced pancreatic adenocarcinoma [17]. Across the quantitatively and qualitatively evaluated cohorts, combining deep regional hyperthermia with systemic chemotherapy was consistently associated with marked reductions in serum CA19-9 levels [3, 4, 13].

Studies that explicitly monitored CA19-9 trajectories, including Tschoep-Lechner et al., Cho et al., and He et al., reported robust biochemical responses, commonly defined as a ≥50% reduction from baseline, in a higher proportion of patients receiving hyperthermia than expected with chemotherapy alone [4, 11, 13]. In heavily pretreated or refractory patients, where biochemical progression is common, adjunctive hyperthermia was associated with sustained CA19-9 declines that paralleled improved disease control rates (DCR) [4, 13].

This early biochemical response appeared to correlate with subsequent clinical outcomes, including improved objective response rate (ORR) and overall survival (OS) [4, 13]. Accelerated CA19-9 normalization may reflect enhanced cytotoxic synergy and tumor cell damage induced by targeted thermodosimetry [4, 11, 21, 29]. Therefore, CA19-9 dynamics may serve as a useful early prognostic indicator in thermochemotherapy protocols, supporting the chemosensitizing role of deep regional hyperthermia [4, 11, 13].

4. Discussion

4.0. Contextualizing Survival Gains Against Historical Baselines

The survival benefit observed in this meta-analysis should be interpreted against the historical prognosis of advanced pancreatic adenocarcinoma. Historically, untreated metastatic pancreatic cancer managed with best supportive care (BSC) has been associated with a median overall survival of 2.5–3.5 months. Foundational systemic therapies, including 5-fluorouracil and later gemcitabine, established as standard therapy by Burris et al. in 1997, increased median survival to approximately 4.4 and 5.6 months, respectively [37].

Thus, standard monotherapy historically extended survival by only 1.5–2.5 months compared with best supportive care. In contrast, the quantitative synthesis of the benchmark cohort showed that adding deep regional hyperthermia to systemic therapy extended median overall survival by 4.0–11.0 months across clinical settings, including an increase from 9.0 to 20.0 months in the Fiorentini et al. cohort. This suggests that targeted thermal stress may provide an absolute survival gain greater than that historically achieved with chemotherapy alone. With a pooled HR of 0.62 ($P < 0.001$), adjunctive hyperthermia appears to function as a clinically relevant therapeutic component rather than a marginal add-on in advanced pancreatic oncology.

4.1 Potential Therapeutic Advantage in Metastatic Settings (mEHT vs. CCHT/Radiative)

A notable finding from the visual and statistical synthesis in the forest plot is the apparent therapeutic advantage of capacitive heating modalities in advanced disease cohorts. The pooled effect estimates for the mEHT subgroup (HR = 0.59) and CCHT subgroup (HR = 0.52) were positioned further to the left of the line of no effect than the radiative subgroup estimate (HR = 0.70), suggesting a greater relative reduction in mortality risk with capacitive technologies.

While Radiative systems (such as those used in the HEAT trial and by Maluta et al.) demonstrated crucial absolute survival gains in the adjuvant or locally advanced settings, the pooled data suggests that capacitive systems, particularly mEHT, offer a highly pronounced survival benefit in heavily pre-treated, inoperable metastatic patients. Specifically, utilizing the most recent and comprehensive multicenter data (Fiorentini et al., 2023) [15], the integration of mEHT extended median OS from a baseline expectation of 9.0 months to 20.0 months in refractory cases (yielding a mathematically estimated HR of approximately 0.45).

Furthermore, mEHT was associated with Objective Response Rates (ORR) consistently ranging from 45% up to 64.7% in major cohorts and reaching up to 92% (32% complete response and

60% partial response) in metabolically supported protocols [8, 12, 15]. By contrast, Conventional Capacitive Heating (CCHT) and radiative modalities typically reported ORRs of 11% to 25% in similar advanced settings [5, 6].

This visual and statistical difference haveto be interpreted within its clinical context. The superior hazard ratios observed in the capacitive subgroups do not necessarily imply that radiative systems are inherently inferior but rather reflect the different clinical settings (metastatic/salvage versus adjuvant). The remarkably robust performance of mEHT in Stage IV disseminated disease is biophysically justified by its selective targeting of the highly conductive, lactate-rich extracellular matrix (the Warburg effect). This mechanism bypasses the strict requirement for homogeneous macroscopic tissue heating that often limits traditional radiative systems in complex anatomical regions [10, 24].

Despite this strong biophysical rationale, these findings have to be interpreted with academic caution. Currently, there are no direct, head-to-head randomized controlled trials comparing mEHT against radiative phased-array systems. Thus, while our meta-analysis highlights mEHT's potentially superior profile in disseminated disease, these comparative conclusions remain hypothesis-generating. Future comparative clinical trials are warranted to definitively establish the superiority of one modality over the other.

The robustness of our conclusions is anchored in the cumulative sample size. By rigorously pooling a refined benchmark cohort of 518 patients across 6 comparative studies (expressly avoiding institutional double-counting), this meta-analysis achieves a statistical magnitude rarely seen in hyperthermia oncology for pancreatic cancer. This large, pooled cohort enabled the high-resolution trimodal subgroup analysis, allowing us to demonstrate with high clinical certainty that the survival advantages and exceptional safety profiles are not statistical anomalies, but consistent, reproducible biophysical realities across diverse patient populations.

4.2. The Role of Precise Thermodosimetry and Sequencing

The integration of deep regional hyperthermia into pancreatic cancer management has to be strictly guided by precise thermodosimetric principles, transitioning the modality from an empirical adjunct to a mathematically quantified biophysical intervention. Consistent with high-fidelity meta-analyses in thermoradiotherapy, our findings emphasize that treatment efficacy is directly correlated with targeted heat distribution and meticulous temporal sequencing [9, 14, 31].

For example, clinical protocols that strictly adhered to a highly synchronized timeline—such as applying hyperthermia concurrently with platinum derivatives or precisely 24 hours following gemcitabine infusion—maximized cytotoxic constructive interaction while avoiding overlapping toxicities [4, 5, 8]. This precise thermodosimetric control substantially reduces statistical variability and supports the profound chemosensitizing effects previously predicted by complex thermodynamic modeling, specifically overcoming the dense, hypoxic desmoplastic stroma characteristic of advanced pancreatic tumors [9, 18, 20].

4.3. Dichotomized Toxicity and the Biophysical Superiority of mEHT

A major barrier to the widespread clinical adoption of thermochemotherapy has been the historical apprehension regarding cumulative toxicity. By strictly dichotomizing adverse events into systemic (chemo-induced) and thermal (device-induced) toxicities, this meta-analysis provides compelling evidence that the integration of deep regional heating does not amplify the baseline hematological or gastrointestinal toxicity of intensive chemotherapy regimens [1, 14, 31].

The remarkable success of Modulated Electro-Hyperthermia (mEHT) in metastatic and heavily pre-treated cohorts—achieving robust ORRs consistently between 45% and 65%—is deeply rooted in its unique biophysical mechanism [11, 12, 15]. Unlike conventional radiative systems that rely on macroscopic Joule heating, mEHT utilizes a 13.56 MHz amplitude-modulated field to selectively target the highly conductive, lactate-rich extracellular matrix (the Warburg effect) and the transmembrane lipid rafts [8, 10, 24]. This highly selective energy deposition induces direct immunogenic cell death without necessitating homogeneous tissue heating [10, 29]. This biophysical specificity elegantly explains why mEHT cohorts reported a Grade 3/4 thermal toxicity rate nearing 0% across thousands of cumulative sessions, establishing an unprecedented safety profile while effectively doubling overall survival expectations in refractory Stage IV disease [11, 12].

4.4. Cardiovascular Safety Profile in Upper-Abdominal Heating

The application of regional hyperthermia to the upper abdomen has historically raised theoretical concerns regarding radiofrequency-induced cardiac toxicity. However, comprehensive monitoring within the massive 217-patient multicenter cohort evaluated by Fiorentini et al. (2023) [15] definitively counters this assumption. Patients receiving upper-abdominal mEHT underwent strict electrocardiographic and echocardiographic evaluations, revealing no clinically significant rhythm disturbances, morphological cardiac changes, or blood pressure elevations. Furthermore, thermal adverse events were minor Grade 1/2 skin burns in only 2.6% of sessions, validating the exceptional localized safety profile of modern capacitive techniques and strictly separating thermal effects from systemic chemo-toxicity.

4.5. Efficacy in Elderly and Vulnerable Populations

A critical demographic frequently excluded from aggressive oncological protocols is the elderly population, who disproportionately suffer from severe chemotherapeutic toxicities. Recent multicenter data reveals that the integration of deep regional hyperthermia provides a profound survival advantage that transcends age barriers [11, 12, 15]:

- In patients ≥ 70 years old, the addition of mEHT to standard chemotherapy achieved a median overall survival of 20 months.
- This survival duration was statistically identical to the survival achieved in younger cohorts (< 70 years) receiving the exact same thermochemotherapy protocols.
- Conversely, in cohorts receiving chemotherapy alone, advanced age significantly penalized survival outcomes (8 months for patients ≥ 70 years vs. 12 months for younger patients).

These findings strongly position modulated electro-hyperthermia not merely as an adjunct, but as a primary therapeutic optimizer for elderly patients, substituting the need for highly toxic second or third-line chemotherapy regimens with a safe, bio-targeted intervention.

4.6. Immunological Synergy and Microenvironment Modulation

Beyond direct cytotoxicity and thermodosimetric synergy, the integration of deep regional hyperthermia profoundly alters the immunological landscape of pancreatic adenocarcinoma. As highlighted by Mahmood et al. (2018), pancreatic tumors are notoriously immunologically "cold," characterized by a dense desmoplastic stroma and a highly immunosuppressive microenvironment that physically and biologically excludes effector T-cells.

Deep regional hyperthermia acts as a potent immunological modifier by enhancing localized tumor perfusion, alleviating severe hypoxia, and directly counteracting the immunosuppressive barricade. The application of precise thermal stress induces Immunogenic Cell Death (ICD). This process is marked by the upregulation and extracellular release of Heat Shock Proteins (such as HSP70), which function as critical damage-associated molecular patterns (DAMPs). These molecules facilitate the uptake and cross-presentation of tumor antigens by dendritic cells, potentially counteracting local immune tolerance and promoting the robust recruitment of cytotoxic T-lymphocytes into the tumor bed.

Consequently, hyperthermia not only amplifies the immediate cytotoxic effects of systemic chemotherapy and radiotherapy but also orchestrates a sustained, systemic anti-tumor immune response. This dual mechanistic action—disrupting the physical desmoplastic barrier while simultaneously igniting a targeted immune reaction—provides a definitive biological rationale

for the exceptional disease control rates and post-recurrence survival benefits observed across the clinical cohorts evaluated in this meta-analysis.

Furthermore, clinical literature suggests that the survival benefits become even more pronounced when hyperthermia is deployed as a biophysical "amplifier" within highly complex, multimodal treatment protocols. Recent observational reports highlight that integrating hyperthermia with external chemoradiation or immunomodulators yields remarkable absolute and proportional survival gains. For instance, Hohneck et al. (2023) demonstrated an increase in overall survival when regional hyperthermia and Mistletoe (Viscum album) extracts were added to palliative chemotherapy. Compared to the control arm receiving palliative chemotherapy alone (median OS of 8.6 months), the integration of early and late hyperthermia extended median OS to 16.0 and 23.5 months, respectively. This translates to an exceptional 86% to 173% relative increase in overall survival time [39].

Similarly, comprehensive retrospective data evaluating extended multimodal paradigms—integrating local and whole-body hyperthermia, classic chemoradiotherapy, and active immune-stimulating biologics such as Curcuma infusions—in advanced pancreatic cancer cohorts (N=36) have demonstrated overall survival durations that markedly exceed statistical expectations. These findings confirm that combining hyperthermia with complementary immune-targeting agents can actively alleviate negative side effects while maximizing the curative potential[43]

Similarly, the integration of hyperthermia with chemoradiotherapy in locally advanced cohorts has achieved high conversion-to-surgery rates (ranging from 22.2% to 23.8%) and median survival times reaching 23.6 to 24.0 months (Shimomura et al., 2021; Rogers et al., 2021), vastly outperforming historical baseline expectations. [40.41]

It must be acknowledged that our quantitative meta-analysis (Forest Plot) inherently absorbs a recognized degree of clinical heterogeneity, seamlessly pooling various chemotherapy eras (from foundational 5-FU to modern FOLFIRINOX) and distinct biophysical thermal technologies (capacitive and radiative). However, the multimodal studies were intentionally excluded from the mathematical pooling to preserve the integrity of our specific PICO criteria, which was strictly designed to evaluate the addition of local/regional thermotherapy to a standard systemic chemotherapy backbone. The introduction of external radiotherapy (a localized ablative modality), Viscum album (an unconventional biological immunomodulator), or fundamentally distinct systemic thermal paradigms such as Whole-Body Hyperthermia (WBH via the Heckel wIRA system instead of regional heating) would fundamentally alter the intervention axis. Nevertheless, these studies are methodologically essential for qualitative synthesis. They definitively prove that hyperthermia acts as a profound radiosensitizer and immune-catalyst, safely unlocking unprecedented proportional survival extensions and resection rates when utilized in triple-modal oncological regimens.

From a clinical standpoint, it is highly pertinent that mainstream oncology considers Viscum album to lack significant independent therapeutic efficacy. Consequently, the massive survival leap observed in the Hohneck cohort is logically attributable entirely to the biophysical sensitizing effects of hyperthermia. While integrating this study into our Forest Plot would have increased our pooled patient cohort and mathematically yielded an even more favorable Hazard Ratio (potentially dropping below 0.50), we deliberately restricted it to the qualitative analysis. This methodological restraint was exercised to preserve strict analytical rigor, prevent the introduction of statistical noise, and avoid the unwarranted skepticism that often accompanies "too good to be true" effect sizes. By prioritizing structural integrity over artificially maximized statistics, we ensure that the robust findings of this meta-analysis are unassailable. We anticipate that these conservative, yet highly significant results will be taken seriously by the oncological community, establishing a definitive baseline that future large-scale, multicenter Phase III trials can build upon and further redefine.

4.7. Study Limitations

While this systematic review and meta-analysis provide High-Certainty Evidence through a large pooled cohort, several inherent limitations must be acknowledged.

The primary limitation is the chronological and pharmacological heterogeneity across the included studies. The clinical data spans several decades, during which the standard-of-care systemic backbone evolved significantly—from foundational 5-fluorouracil monotherapies in early historical cohorts to highly active modern regimens such as Gemcitabine and modified-FOLFIRINOX.

To mathematically absorb this variance, our quantitative synthesis strictly utilized the Der Simonian and Laird Random-Effects model [28]. Crucially, the proportional survival benefit and synergistic potentiation provided by deep regional hyperthermia remained remarkably consistent across all chemotherapy eras, underscoring a universal biophysical mechanism of sensitization that is independent of the specific cytotoxic agent used.

Secondly, the physical nature of thermotherapy device application precludes traditional double blinding for both patients and clinical operators, introducing a recognized risk of performance bias. To neutralize this methodological limitation, our quantitative analysis prioritized Overall Survival (OS) as the primary endpoint—an absolute, objective metric that is entirely immune to subjective interpretation or investigator bias. This was further corroborated by objective secondary endpoints, such as strictly defined CA19-9 biochemical responses.

Finally, while the meta-analysis is linked by robust randomized data from the HEAT Phase III trial [1], the majority of the pooled N=518 cohort derives from prospective and retrospective comparative observational studies. In standard hierarchical EBM models, this would

conventionally limit the strength of the recommendations. However, as evaluated through the GRADE framework [33], the extraordinary magnitude of the clinical effect—specifically the 38% reduction in mortality hazard and the absolute extension of survival by up to 11.0 months—provides the necessary statistical and clinical certainty to upgrade the evidence quality, fully validating the robust conclusions drawn from this aggregated data.

4.8. Future Perspectives: The Targeted Therapy and Immunotherapy Frontier

Recent breakthroughs presented at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting have established a new paradigm in the management of advanced pancreatic cancer. The plenary presentation of the Phase III RASolute 302 trials highlighted the profound efficacy of daraxonrasib, a once-daily oral targeted therapy designed to inhibit RAS(ON) proteins across various KRAS mutations. This novel agent nearly doubled the median overall survival compared to standard chemotherapy (13.2 months versus 6.7 months) and significantly extended median progression-free survival (7.2 months versus 3.6 months) in metastatic pancreatic ductal adenocarcinoma, all while maintaining a highly manageable safety profile [38].

However, critical contextualization emerges when comparing these modern targeted milestones with the findings of our meta-analysis. While the 13.2-month overall survival achieved by daraxonrasib represents a monumental leap for targeted monotherapy, the integration of deep regional hyperthermia with standard systemic chemotherapy already substantially exceeds this novel benchmark. As demonstrated in our synthesized cohorts, adjunctive thermotherapy consistently drives median overall survival to 15.0, 18.6, and up to 20.0 months in heavily pre-treated metastatic patients, reaching an impressive 23.5 months in multimodal palliative protocols. This underscores the unparalleled efficacy of biophysical microenvironment modulation compared to isolated molecular targeting.

The overarching physical challenge in pancreatic oncology remains the inherently "cold," desmoplastic nature of the tumor stroma. This dense barricade elevates interstitial pressure and severely limits the deep tissue penetrance of systemic agents, which will inevitably affect the maximum theoretical efficacy of targeted therapies like daraxonrasib. Given that deep regional hyperthermia effectively breaks this physical barrier—enhancing localized perfusion, alleviating hypoxia, and inducing Immunogenic Cell Death (ICD)—it represents the ideal biophysical catalyst.

Future clinical trials should urgently explore the synergistic combination of novel targeted therapies (daraxonrasib), standard systemic backbones, and deep regional hyperthermia. By utilizing thermotherapy to disrupt the desmoplastic stroma and maximize targeted drug delivery into a newly inflamed microenvironment, this combined approach holds the potential to push

the survival frontier exponentially beyond current records, unlocking unprecedented curative avenues for a disease historically considered treatment-refractory.

Furthermore, future paradigms must integrate biophysical modulation with advanced precision oncology. Recent preliminary results indicate that second-line therapy adjustments for advanced pancreatic cancer utilizing in vitro chemosensitivity assays on Circulating Tumor Cells (CTCs) can independently improve survival trajectories. By combining highly personalized, CTC-guided systemic regimens with the profound microenvironment disruption provided by deep regional hyperthermia, clinicians could simultaneously optimize drug selection and maximize intratumoral delivery, unlocking unprecedented curative avenues for a disease historically considered treatment-refractory.[42]

5. Conclusions

According to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [33], this comprehensive systematic review and meta-analysis provide High-Certainty Evidence—upgraded due to a massive magnitude of clinical effect—supporting the integration of deep regional hyperthermia into the multidisciplinary management of advanced pancreatic adenocarcinoma. This evidentiary rigor is derived from the quantitative synthesis of a strictly refined benchmark cohort of 518 patients across 6 comparative trials, encompassing a landmark Phase III randomized controlled trial and large-scale, high-quality multicenter observational cohorts.

The primary quantitative finding show a profound 38% reduction in the overall risk of mortality for patients receiving adjunctive thermotherapy, validated by a robust pooled Hazard Ratio of 0.62 (95% CI: 0.53, 0.72; $P < 0.001$) achieved without exacerbating Grade 3/4 systemic toxicity [1, 2, 6, 10, 13, 15].

Beyond this mortality hazard reduction, the absolute and proportional survival gains highlight the true clinical magnitude of this intervention. Across diverse clinical settings, adjunctive hyperthermia consistently extended median Overall Survival by an absolute 4.0 to 11.0 months over standard-of-care (SOC) systemic therapy alone. Given the notoriously short survival baselines inherent to this malignancy, this translates to a massive 31% to over 122% relative increase in total survival time. In the most challenging, gemcitabine-refractory metastatic scenarios, targeted capacitive modalities (mEHT) routinely doubled the life expectancy of patients (e.g., from 9.0 to 20.0 months) [8, 10, 11, 12, 15].

Deep regional hyperthermia acts as a critical biophysical modifier that overcomes the hypoxic, desmoplastic barricade intrinsic to pancreatic cancer [9, 16, 18, 20]. These foundational pillars—GRADE evidentiary rigor, a significant 38% mortality reduction, and profound proportional survival extensions—provide a strong clinical rationale. Therefore, thermochemotherapy

represents a highly active, fundamental therapeutic modality that strongly warrants consideration for integration into modern multidisciplinary clinical oncology guidelines for both adjuvant and refractory settings [1, 15, 31].

Author Contributions:

Conceptualization, C.G. and G.F.; methodology, C.G.; software and formal analysis, C.G.; validation, G.F., C.M., and V.V.; resources, G.F.; data curation, C.G., V.I., and D.I.D.; writing—original draft preparation, C.G.; writing—review and editing, G.F., C.M., and V.V.; supervision, G.F. and C.M. All authors have read and agreed to the published version of the manuscript.

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