Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report[1]

Clinical hyperthermia alongside radiotherapy and/or chemotherapy for recurrent breast cancer

What is a Topic Exploration Report?

Topic Exploration Reports are not health technology assessments. These reports provide a high-level briefing on new topics submitted to Health Technology Wales and are not based on exhaustive or systematic literature searches. Instead, they rely on a focused scan of key resources.

What evidence is used in a Topic Exploration Report?

Priority is given to summarising the most relevant or useful evidence, rather than covering all possible evidence. Information reported is typically based on abstracts and study authors' own conclusions, rather than detailed scrutiny of full texts.

What are the aims of a Topic Exploration Report?

Topic Exploration Reports offer an overview of the available evidence on a topic and aim to highlight any uncertainties or gaps in the evidence. These reports outline the quantity and type of evidence found, but no critical appraisal or formal evidence synthesis is conducted.

How should a Topic Exploration Report be used?

Topic Exploration Reports can be used to indicate what evidence may be available for a topic, and do not provide definitive guidance on how a technology should be used. The evidence presented within the reports should be interpreted with caution.

[1] Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg
Translation of published technical HTW documents from English into Welsh

Topic exploration report number	TER652
Topic	Clinical hyperthermia alongside radiotherapy and/or chemotherapy for recurrent breast cancer
Summary of findings	Clinical hyperthermia is a heat treatment used in addition to radiotherapy and/or chemotherapy. Its purpose is to make tumour cells more sensitive to treatments. The subset of cancers with reduced sensitivity to radiotherapy and chemotherapy including recurrent or previously irradiated tumours, would benefit most from this treatment. One Dutch guideline, three systematic reviews, one randomised controlled trial, five retrospective studies, and four ongoing studies were identified on the effectiveness of hyperthermia as an add on to radiotherapy during recurrent breast cancer treatment. There was considerable overlap in the included primary studies across two systematic reviews, and they were published between 1981 and 2017. The primary studies included in the most recent systematic reviews were mostly single arm studies with some RCTs directly comparing reirradiation plus hyperthermia with reirradiation alone. The primary studies also varied considerably with high heterogeneity. We did not identify any cost-effectiveness data. One systematic review found that hyperthermia with radiotherapy is associated with a higher complete response rate, but higher risk of toxicity versus radiotherapy alone. Another systematic review found that high thermal dosages are associated with more complete responses than patients who receive low thermal dose and concluded that thermoradiation therapy enhances the likelihood of complete response rates in locally recurrent breast cancers over radiotherapy alone by 22% with minimal acute and late morbidities. The key uncertainties noted were that the recent systematic reviews included mostly single-arm or non-randomised studies and that older studies may use differing radiotherapy techniques and hyperthermia equipment to what is currently offered in practice. Within the systematic reviews, there was variation in the thermal dose, temperature targets, duration, frequency, and sequencing of hyperthermia in relation to radiotherapy.

Introduction and aims

Clinical hyperthermia is a heat treatment used in addition to radiotherapy and/or chemotherapy. Its purpose is to make tumour cells more sensitive to treatments. It involves the controlled heating of tumour tissue, typically to 40–43 °C, delivered locally or regionally using electromagnetic, radiofrequency, microwave, or ultrasound-based systems. It is usually administered immediately before or after radiotherapy or chemotherapy. Clinical hyperthermia works in several ways. It improves oxygenation and blood flow, inhibits DNA damage repair, meaning radiation induced DNA damage is less likely to be repaired, and it directly weakens tumour cells.

Hyperthermia is not appropriate for all cancer patients. Some cancers show reduced sensitivity to radiotherapy and chemotherapy due to factors such as tumour hypoxia, large tumour volume, intrinsic radio resistance, or prior irradiation limiting further dose escalation. This is particularly relevant in locally advanced or high-risk tumours, bulky or hypoxic tumours, bony and soft tissue metastases, and recurrent or previously irradiated tumours, and tumours near radiosensitive organs (e.g., close to bowels or nerves) such as soft tissue tumours near neurovascular structures. These subgroups would benefit most from hyperthermia.

Information from the topic proposer details multiple available CE marked systems (such as ALBA systems by Medlogix). The topic proposer suggests that the implementation of clinical hyperthermia would not require full time staffing or a permanent dedicated space because a single radiographer delivers the treatment in a review room. Hyperthermia is currently offered in Guy's and St Thomas' NHS Foundation Trust, although only wIRA (water-filtered infrared) hyperthermia is currently offered, with limited clinical application due to its superficial delivery (up to approximately 15mm).

After narrowing the scope of the topic suggestion, Health Technology Wales researchers searched for evidence on the effectiveness of clinical hyperthermia as an add on to radiotherapy or chemotherapy for recurrent breast cancer.

Evidence overview

HTW has previously published TER644: Water-filtered infrared radiation hyperthermia for the treatment of locally recurrent breast cancer. This was limited to one specific technique of delivering hyperthermia.

Guidelines

A Dutch breast cancer guideline published in 2012 was identified via the topic proposer (NABON 2012). The guideline refers to evidence supporting the effectiveness of hyperthermia with radiotherapy when compared to radiotherapy alone. The guideline stated that in cases of locoregional recurrence of breast cancer after mastectomy in a previously irradiated area, low-dose re-irradiation with hyperthermia leads to a better local control than re-irradiation only (section 8.2.3).

Systematic reviews

Three systematic reviews were identified which were published in 1996 (Vernon et al. 1996), 2016 (Datta et al. 2016) and 2019 (Bakker et al. 2019). Most of the studies referenced in Bakker et al. (2019) were also referenced in Datta et al (2016). The included primary studies in Datta et al. (2016) and Bakker et al. (2019) were published between 1981 and 2017. The primary studies were mostly single arm studies with some randomised controlled trials and non-randomised trials.

Evidence overview

The primary studies varied considerably, including the study population, the duration of follow-up, radiotherapy dosage, the interval between primary radiotherapy and reirradiation, and the sequencing of hyperthermia (before or after reirradiation). Differences in the administration of hyperthermia also varied, including variations in the average temperature, duration, and fractions. Outcomes across the reviews included complete response rate (CR), thermal toxicity, local control, and overall survival.

Bakker et al. (2019) investigated whether there is a relationship between achieved hyperthermia dose and clinical outcome and thermal toxicity for patients with recurrent breast cancer treated with hyperthermia and radiotherapy. Based on abstract findings, patients who received high thermal dose had on average 34% (range 27%–53%) more complete responses than patients who received low thermal dose, however, a higher temperature increased the incidence of thermal toxicity.

In Datta et al. (2016), a CR of 60.2% was achieved with hyperthermia and radiotherapy versus 38.1% with radiotherapy alone (odds ratio 2.64, 95% confidence interval [CI] 1.66 to 4.18, p<0.001). Mean acute and late grade 3/4 toxicities with hyperthermia and radiotherapy were 14.4% and 5.2%, respectively. Datta et al. (2016) concluded that thermoradiation therapy enhances the likelihood of CR rates in locally recurrent breast cancers over radiotherapy alone by 22% with minimal acute and late morbidities. For those previously irradiated, reirradiation with hyperthermia provides locoregional control in two thirds of the patients.

Vernon et al. (1996) published a systematic review of five RCTs published between 1988 and 1991 which included 306 participants with advanced primary or recurrent breast cancer. Outcomes included local complete response, time to local failure, distant progression and survival, and treatment toxicity. The overall complete response rate for hyperthermia as an adjunct to radiotherapy was 59%, compared with 41% for radiotherapy alone. Information from the topic proposer suggests that the hyperthermia systems used in studies from the 1980s and 1990s operated with rudimentary single-element microwave applicators and limited thermometric feedback, and that modern systems are more capable of achieving and maintaining therapeutic temperatures uniformly across the target volume.

Retrospective studies

An additional five retrospective cohort studies published between 2018 and 2025 were identified (Dharmaiah et al. 2019, Notter et al. 2020, Oldenborg et al. 2018, Oldenborg et al. 2019, Tello Valverde et al. 2025) evaluating reirradiation combined with hyperthermia for locoregional or locally recurrent breast cancer. Overall, the retrospective studies were limited by their non-randomised, single arm designs, with no direct comparison to reirradiation alone. Across studies, there was substantial heterogeneity in patient populations, radiotherapy regimens, and hyperthermia techniques which limits direct comparability across studies. The studies varied substantially in size (36 to 201 patients), setting (United States, Switzerland, and the Netherlands), and clinical context, including unresectable recurrences, postoperative reirradiation, and extensive chest wall disease such as breast cancer en cuirasse. Outcomes included clinical response, local control, progression-free outcomes, survival, and treatment-related toxicity. Reported clinical response rates were generally high (approximately 60–70%), while local control and progression-free outcomes were strongly influenced by tumour burden, disease characteristics, and thermal dose. Rates of grade 3 or more acute and late toxicity varied widely between studies and appeared sensitive to radiotherapy regimen and hyperthermia delivery.

Ongoing studies

Evidence overview

Four ongoing studies were identified.

A published protocol on the HISTOTHERM study was identified (Thomsen et al. 2023). The study is an ongoing prospective longitudinal study evaluating the response to combined mild local hyperthermia and low dose hypofractionated re-irradiation in adults with inoperable, locally or locoregionally recurrent breast cancer after prior mastectomy and radiotherapy. Approximately 40 patients are being enrolled at the University Medical Centre Freiburg, with recruitment ongoing since 2019 and expected to conclude around 2025, followed by up to five years of follow-up. The study population includes patients with macroscopic superficial tumours (≤20 mm depth), with distant metastatic disease permitted. Outcomes will include local tumour response, identification of predictive and prognostic biomarkers, immune and proteomic response profiles, quality of life, local control, distant metastasis-free survival, and overall survival.

Another ongoing study is a prospective non-comparative study in the UK (NCT06659146) evaluating the safety and efficacy of wIRA in addition to standard-of-care palliative radiotherapy in patients with incurable or inoperable cancer with superficial lesions, including head and neck (group 1), skin (group 2) and locally recurrent breast cancer (group 3). Hyperthermia will be delivered by using the Hydrosun-TWH1500 system (Hydrosun Medizintechnik, Müllheim, Germany) to the treatment area before radiotherapy. The study will assess the following outcomes: (1) response rates (best objective and duration), (2) toxicities, (3) progression-free survival, (4) overall survival, (4) QoL.

The topic proposer identified the RT-HYPE study which is an ongoing multicentre prospective cohort study currently open at nine Dutch centres, with a target enrolment of 500 participants. The study will evaluate postoperative re-irradiation with or without hyperthermia in people with locoregional recurrent breast cancer. Outcomes include patient-reported toxicity, locoregional control, quality of life, and overall survival at two and five years. The estimated completion date is unclear, although the study is still actively recruiting as of May 2026.

An ongoing prospective observational study registered in the USA is estimated to complete in January 2027. See overleaf for further details.

Areas of uncertainty

- We did not identify any cost-effectiveness data.
- Since the review published in 1996, there has been changes in breast cancer treatment.
- The recent systematic reviews include mostly single-arm or non-randomised studies, with some randomised controlled trials.
- Some primary studies included within the evidence base are dated and may use differing radiotherapy techniques and hyperthermia equipment to what is currently offered in practice. Information from the topic proposer suggests modern therapies deliver radiation with greater conformality and sparing of surrounding tissues than the techniques used in earlier studies.
- Based on the evidence base in this TER, there was variation in the thermal dose, temperature targets, duration, frequency, and sequencing of hyperthermia in relation to radiotherapy.

Areas of uncertainty
Information from the topic proposer details the optimal therapeutic window is between 41 and 43 degrees within a 60-minute session. • Within the recurrent breast cancer subgroup, some groups may benefit more from hyperthermia (e.g. tumour burden, extent of chest wall disease, prior radiation dose, time since previous irradiation). Information from the topic proposer details locally recurrent breast cancer in a previous irradiated field, unresectable or irresectable disease, smaller tumours (less than 5 cm) for curative intent, and hypoxic/radio-resistant tumours for palliation are identified within the evidence base as being the populations with highest benefit. • Different hyperthermia devices maybe more effective than others.

Literature search results

Health technology assessments and guidance
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Date of search	28 April 2026
Concepts used	clinical hyperthermia or hyperthermia AND breast cancer OR recurrent breast cancer

Proposed research question and evidence selection criteria (if selected)

Proposed Research question	What is the clinical and cost-effectiveness of clinical hyperthermia when added to radiotherapy during reirradiation of recurrent breast cancer?

	Inclusion criteria	Exclusion criteria
Population	Adults with locally recurrent breast cancer who have had radiotherapy or chemoradiotherapy (whole or partial breast irradiation)	
Intervention	Clinical hyperthermia and standard care (radiotherapy OR chemoradiotherapy)	First line radiotherapy treatment
Comparison/ Comparators	Standard care alone	
Outcome measures	Overall survival, progression-free survival, distant metastasis-free survival Local control, local recurrence rate Time to local progression Patient-reported outcome measures (e.g., symptom control, reduction in pain, bleeding) Adverse events including thermal toxicity Health related QoL Resource use Economic outcomes	

Proposed speciality	**Cancer**