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Original Article

The use of hyperthermia to overcome tumour hypoxia in the treatment of advanced breast cancer

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Abstract

Purpose: The purpose of this review was to explore the literature on the use of hyperthermia (HT) in advanced breast cancer.

Methods: A literature search was conducted to obtain information from recent trials of HT and/or chemotherapy (CH) and radiotherapy (RT) for patients with locally recurrent breast carcinoma. Issues concerned with patient compliance and side effects have also been reviewed and future recommendations for research made.

Results: Results of recent trials have demonstrated promising outcomes for HT and RT in combination, particularly for recurrent disease to improve local control (LC). There is no evidence, however, to support a positive effect on overall survival.

Conclusions: Despite positive results HT has not been widely embraced, due to financial and logistical limitations. Future recommendations include larger, randomised, controlled studies and the development of temperature mapping to avoid potentially limiting HT blisters.

Keywords

Advanced breast cancer; Hyperthermia; hypoxia; thermoradiation

INTRODUCTION

Even after radical treatment local recurrence occurs in 15–30% of breast cancer patients, giving a mean 5-year survival of 30–50% for this group.[1] Current treatment of locally advanced breast cancer has a multi-disciplinary approach including surgery, radiotherapy (RT), chemotherapy (CH) and hormone therapy. Local control (LC) and survival rates, however, are not impressive.

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Without treatment, locally advanced disease can cause pain, ulceration, bleeding and arm oedema in as many as 62%[2]; therefore, investigating new approaches is necessary to improve quality of life for these patients.

CH has little effect on LC and 40% still recur with RT.[3] Tumour hypoxia (tissues with limited oxygen) also contributes to resistance to RT and CH[4] as cells require oxygen to respond to these treatments. This suggests a need for other modalities and hyperthermia (HT) is a potential option.

HT is the application of heat to increase the tumour temperature, and therefore oxygenation. Breast cancer is an ideal treatment site for this as lesions are superficial, thus heating is easy to achieve.[5]

HT acts as a radiosensitiser, that is, by enhancing the sensitivity of tumour cells to the killing effects of ionising radiation and CH drugs.[5] Its use can be divided into three domains: whole body, regional and local. For advanced breast cancer local HT is the treatment of choice, heating the breast only.

In a historical overview, Corry and Armour[6] claimed that it is cells in tumours rather than tumour cells that are sensitised to heat. This discovery has direct clinical impact and explains why HT alone is not an effective cancer treatment. They also concluded that the target temperature should be 41–42°C rather than the 43°C initially thought effective in early in vivo experiments. This may explain why initial HT trials gave disappointing results and unfortunately meant that HT research was slow to be expanded in the clinical setting.

Aims

The aim of this paper is to provide a critical evaluation of the literature on the use of HT in advanced breast cancer. Specifically the review will:

1. Outline the rationale for HT.
2. Identify the feasibility of HT in standard treatment regimes and its implications on the patient, department and service.
3. Discuss patient compliance and the impact on the use of HT.
4. Make recommendations to inform future practice.

LITERATURE REVIEW

A comprehensive literature search was conducted using the online CINAHL, MEDLINE and COCHRANE databases, and library material to access key journals. See Appendix 1 for selection criteria. Nineteen articles were reviewed, twelve of which are clinical trials. These are summarised in Table 1.

Rationale for the use of HT

It is well known that HT causes and enhances direct tissue damage, cell killing and inhibits DNA damage repair. Although cells in the late S-phase of the cell cycle are most resistant to ionising radiation, it is here where they are most sensitive to HT[7] and can therefore be used to potentiate radiation effects.

HT also induces tumour re-oxygenation: solid tumours have a poor blood supply, making them anoxic. This means they are radio resistant and harder to kill, thus increasing the chances of metastasis, giving a poorer prognosis. As tumour cells cool slowly when heated, their nutrients

Table 1. *Main characteristics of HT trials for advanced breast cancer*

References	Study type	Sample size	Treatment 1	Treatment 2
ICHG, 1996[10]	PH3 RCT Multicentre	306	CONV RT	RT/HT
Sherar et al., 1997[15]	PH3 RCT Multicentre	276	CONV RT	RT/HT
Jones et al., 2005[16]	RCT	109	CONV RT	RT/HT
Welz et al., 2005[3]	RCT	50	RT/HT (10 therapy)	RT/HT (for reccurance)
Kapp et al., 1992[7]	PH 1/2	89	N/A	RT/HT
Li et al., 2004[12]	PH 1/2	73	N/A	RT/HT
Feyerabend et al., 2001[2]	PH 1/2	25	N/A	RT/HT/CH
Jones et al., 2004[1]	Prospect trial	18	N/A	RT/HT/CH
Hehr et al., 2001[13]	Retro anal	39	N/A	RT/HT
Ben-Yosef et al., 2004[11]	Local report	15	N/A	RT/HT
Fujimoto et al., 2003[18]	Pilot	9 (Pre-operation)	N/A	Hyperthermic tumour ablation with post-operation RT
Yokoyama et al., 2005[19]	Case report	1	N/A	RT/HT

CH, chemotherapy; HT, hyperthermia; ICHG, International Collaborative Hyperthermia Group; N/A, not applicable; RT, radiotherapy; RCT, randomised controlled trial; CONV RT, conventional radiotherapy.

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and oxygen are cut off and their vascular system breaks down. The hypoxic area of the tumour decreases and mean temperature rises will be greater.[5] Any hypoxic cells that still exist in the tumour are in areas of low pH and these cells are much more sensitive to heat damage by HT.

The effects of HT are dependent upon temperature, following in vitro experiments, 40–44°C was seen to be cytotoxic for tumour cells. This means when RT and CH are less effective HT can add to and enhance their effects at increased temperatures.[8] If HT is delivered too frequently, however, a phenomenon known as thermo-tolerance occurs and the tumour becomes resistant to its cytotoxic effects. HT treatments are therefore usually separated by gaps of a week.

HT has been described as the best hypoxic sensitiser discovered to date and has a powerful rationale as it lacks the systemic toxicities of CH.[6]

HT technique

Generally local HT is applied using microwave, ultrasound or electromagnetic energy via an applicator (often a water bolus) placed over the treatment volume. The energy is distributed throughout the volume and increases the temperature of the tissues and tumour. Thermometry is achieved using catheters or probes placed under the skin, and temperature is controlled by the power output of the system. Quality assurance guidelines have been produced regarding the use of the equipment.[9]

In the literature, the range of frequencies used varied, from 210 to 915 MHz. Kapp et al.[7] found that the effective heating depths of frequencies 434–915 MHz is 1–3 cm, which corresponds to the soft-tissue thickness of the breast following mastectomy. This means the tissues at risk are adequately heated, sparing those underneath (i.e., lung and heart) and is therefore the desired range of frequencies to be used. This means that patients must have had radical surgery for these treatments to be effective.

Results of studies and critique

Results shown in Table 2 demonstrate an additive effect of HT combined with RT for locally recurrent breast cancer. The largest trial by the International Collaborative Hyperthermia Group (ICHG)[10] showed convincing results in only one of two phase 3 studies to date. They concluded that HT was well tolerated without significantly adding to acute or long-term toxicity but their results only confirmed its use with

Table 2. *Summary of RT/HT protocols use d*

References	RT dose (Gy/#)	HT temperature (°C)	HT TIME (min)	HT (frequency/wk)	No. of HT TRT's	Pre/post RT	CH
10	60/30	43	60	NI	2–8	NI	N/A
15	74/37 rad 30/15 pall	43	30–60	NI	2–8	NI	N/A
16	66/33 rad 30/15 pall	50	1–2 h	2	Max 10	NI	N/A
3	60/30	41	60	2	Median 11	Pre	N/A
7	42.4/	42.8	45	2	1–6	NI	N/A
12	59.5/30 rad 43 Gy pall	43.6	30–60	Average 1.5	Average 4.5	30–60 min post	N/A
2	50/25	43	60	1	4	Max 30 min post	Epirubicin Ifosfamide
1	50/25 + 15 Gy booster	41.5	60	2	10	Max 30 min post	Taxol
13	50/25	41	60	2	Median 7	Pre	N/A
11	30/15	45	45	Min 2 day gap	2	Max 10 min post	N/A
18	50/25	50 min	30	Over 7–14 days	1.4 average	Pre-operation	N/A
19	60/30	39.5	40	1	5	NI	N/A

CH, chemotherapy; HT, hyperthermia; N/A, not applicable; NI, no information; pall, palliative; RT, radiotherapy.

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Table 3. *Main clinical findings*

References	LC (%)	CR (%)	Side effects	Statistical significant results?	Other parameters affecting LC
10	41 RT; 59 RT/HT	N/A	11% blisters, 7% ulcers RT/HT, 2% RT	Yes, LC ($p = 0.007$)	Lesion size, depth, RT dose, mets
15	N/A	41 RT; 61 RT/HT	Not discussed	Higher thermal dose sig with CR, prev RT not sig	Systemic disease, concurrent hormone therapy, initial T stage, thermal dose
16	N/A	42.3 RT; 66.1 RT/HT	46% burns	95% CI	Best response if prev irradiated (68.2% vs. 23.5%)
3	80	N/A	16% grade 3 toxicity, 14% blisters	Prev RT not sig	NI
7	68	N/A	45% pain, 5% blisters	RCT warranted to confirm value	Oest rec status, initial T stage, age, RT dose, time from diag–1st fail
12	N/A	56	40% blisters	Prev RT not sig, HT benefit sig	Tumour type
2	80	44	5% skin tox, 40% marrow tox	Marrow tox sig	Non-inflam disease did better
1	50	33	5% burn	NI	NI
13	Median 53 at 2 y	N/A	21% blisters	LC ($p = 0.09$)	Tumour resectability, RT dose
11	N/A	75	20% major ulceration	NI (report only)	NI
18	100 post operation	N/A	Well tolerated	Reduction rate sig	NI
19	N/A	100 at 33 mo	None reported	1 pt only	NI

CI, confidence interval; CR, complete response; LC, local control; NI, no information; sig, significant; tox, toxicity; prev, previous; oest rec, oestrogen receptor; diag, dignosis.

palliative RT. Their best results from RT/HT were seen in patients who had been previously irradiated, where complete response improved from 38 to 78%. Their findings were confirmed by later trials as shown in Table 3.

Despite the important nature of this trial to produce the largest set of results, this paper has been highly criticised. First, in combining the results from five separate trials, a lack of homogeneity exists in the patient selection criteria (tumours with different prognoses, size and depth). RT schedules also varied in dose per fraction, fractions per week, overall treatment time and RT dose. Likewise, there were significant variations in HT treatments in terms of equipment frequency (affecting the treatment depth), different margins, number/duration of HT treatments and the interval between RT and HT. Each of these may have affected the prognosis and demonstrates why results varied considerably between centres for this trial.

Most studies, however, agreed with the results of the ICHG trial, although the majority made no comparison with RT alone, looking only at HT/RT in combination. This means using historic data for results of RT outcomes from other studies and lack of a control group. This means it is difficult to estimate the size of the effect of HT treatment. The heterogeneity of patient characteristics, trial variables and measured end points has also made accurate correlations of these studies impossible. Difficulty arises in accurately comparing the range of study designs, such as results from a case study being compared to an RCT.

The quality of HT treatment is questioned in the study by Ben-Yosef et al.[11] as no accurate temperature measurements were taken within the tumour. Similarly in the study by Kapp et al.,[7] 98% of the 89 patients had only one or two HT treatments, therefore can this be accepted as a treatment regime or was the HT not making any difference? The authors felt a phase 3 study was warranted to confirm its value. No study proposed an optimum HT method or regime, and as a result is highlighted as an area for future trial work.

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Several studies compared the response of different histologies amongst those trialled. Li et al.[12] concluded that small, nodular tumours responded quicker than bulky/diffuse disease, but tended to recur later within the treatment field. Feyerabend et al.,[2] however, concluded that those with non-inflammatory disease showed better results.

In each of the studies several other parameters were identified as significantly affecting LC. These were tumour size and depth, evidence of metastasis[10] tumour resectability[13] oestrogen receptor status, initial T stage, time from diagnosis to first failure,[7] RT dose.[7,10,13] The strong radiation dose relationship, cited by these authors, attempts to explain some of the variations found in the range of LC rates reported. Again, this requires further investigation as variations were also found concerning median follow-up times and total radiation doses.

Triple modality results

Feyerabend et al.[2] performed the larger of the tri-modality trials, the principal conclusion that combination RT/HT and CH is feasible with acceptable toxicity. The authors failed to confirm, however, that the addition of CH was advantageous over RT/HT alone. The complexity of this type of treatment regime makes any evidence difficult to interpret and a larger study would be beneficial in the future.

The second paper[1] assessing the addition of CH also agreed it was feasible with reasonable toxicity although a proportion of these patients also received hormone therapy, questioning the validity of the result. In addition, they concluded that re-oxygenation is more relevant for tumour response than cytotoxic effect and that HT induced the re-oxygenation for at least 24 hours. This was, however, temperature dependent and requires further investigation.

Side effects and patient compliance

Due to the different assessment scales and HT techniques used in the studies detailed comparative analysis is not possible. It is possible, however, to highlight some of the main trends. Several studies considered patient compliance or treatment toxicity as secondary end points and this was, on average, found to be low for RT/HT regimes in combination. Burns blisters and ulcers were described as typical HT side effects.

In the largest trial[10] HT was generally well tolerated, although a small number of patients had their treatment stopped due to pain. Overall 11% developed blisters in the HT/RT group compared with 2% in the RT only arm, although different toxicity scales were used to measure them in each of the centres. This result can be questioned as comparisons cannot be made between the severity of skin reactions at the five centres.

In an older study,[7] a higher proportion of patients (45%) noted pain although all completed their treatment. This was decreased by lowering the power output, a common method cited in the literature.[7,12] Five percent also developed blisters and they concluded that pain was a major compromise in achieved HT temperatures. These results may lose relevance as it has also been found that advanced HT technology has dramatically lowered the incidence of pain and blistering[8] and improved clinical outcome. This paper noted the frequency of skin burns was higher when using a radiofrequency capacitive heating technique (5–16%) compared with a radiative technique (0–3%). No definite conclusions were drawn in the literature although others suggested similar views, a topic for further investigation.

In a more recent study[11] non-invasive thermometry was trialled, despite being a small study ($n = 15$), although three patients had problems with ulceration treatment was very well tolerated. Welz et al.[3] also found HT well tolerated although 15% had their treatment stopped. Feyerabend et al.[2] agreed that skin toxicity was low, although most experienced mild or moderate discomfort often requiring analgesia. No patients stopped treatment but many variables were present in their patient selection and the sequence and timing of therapy given, making it difficult to draw valid conclusions. Hehr et al.[13] cited comparable data in terms of patient compliance. Twenty-one percent had their HT

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stopped due to blisters, and a third of patients experienced grade 3 toxicity. No radiation reactions caused abandonment of the course.

Some patients may not be able to feel hot spots, as tissue can become desensitised following surgery,[8] others may be reluctant to mention unpleasant sensations or will tolerate higher levels of pain, knowing the importance of completing treatment. Li et al.[12] support this theory as, although treatment was not suspended in any of the study sample, two required skin transplants to close ulceration caused by heating.

Sugarbaker et al.[14] used an anaesthetic skin gel to alleviate skin pain, combined with a pre-treatment oral narcotic. Only 2 of the 238 treatments were not completed due to patient discomfort, demonstrating the effective use of pain relief to achieve treatment goals. Jones et al.[1] also found local anaesthesia and Lorazepam effective as only 5% of the study sample ($n = 1$) had treatment stopped.

The literature suggests that local HT is mainly limited by blisters and patient discomfort. The risk is related to heating technique used and can be alleviated by a reduction in power.

Effect of thermal dose

Sherar et al.[15] conducted a trial considering the effect of thermal dose. Although data were combined from several centres, using different measurement techniques, overall they concluded that HT dose was associated with complete response. Multivariate analysis showed systemic disease was independent of this, demonstrating that 'good' HT is of direct benefit.

Jones et al.[16] also looked at HT dose in terms of cumulative equivalent minutes (CEM) for superficial tumours at several anatomical sites. They concluded that adjuvant HT with a thermal dose of more than 10 CEM 43°C T_{90} conferred a significant LC benefit when combined with RT. A potential flaw is that tumours were initially assessed for 'heatability'. Only those that would achieve the minimum effective dose were randomised which may have biased the results.

DISCUSSION

In recent years, research has shown promising outcomes for the use of HT as demonstrated in this literature review. Several limitations and recommendations have been identified however, and will be discussed in this section.

Implications of HT on the patient, department and service

Many reasons are evident for the limited use of HT. Supplying a department with HT equipment would benefit a relatively small proportion of patients, raising economic issues in NHS hospitals where budgets are limited. The technology is not widely available and requires expert staff (including a nurse and a clinician with knowledge of HT) that would need to train others.

As a procedure it is labour-intensive in comparison to RT, each treatment is time consuming and staff must carefully monitor the patient while managing the equipment. Second, the need for a strict time schedule between RT and HT could be an issue in busy departments, particularly in times of machine breakdown.

If there is a service demand following results from future clinical trials regional centres may specialise in HT, allowing for larger randomised controlled trials to be conducted.

For the patient, there are two main implications. First with the lack of technology available they may need to travel away from family to the centre, which is not ideal. Second, issues concerning patient discomfort and decreasing the incidence of blistering should be addressed. Monitoring is vital to ensure the patient copes with the procedure and that changes can be made to the HT temperature.

FUTURE RECOMMENDATIONS

The use of thermometry and temperature mapping

In order to effectively evaluate the quality of HT, measurement of actual temperature distribution within the tumour is important and will

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allow for better control of HT applications. Temperature mapping (the production of a 'treatment plan' of the heat distribution within the volume) is also recommended to avoid potentially limiting HT blisters. The use, therefore, of a thermal isoeffect dose would allow trial data to be more easily compared and allow thorough clinical evaluation of the quality of HT.[17]

One paper also suggested looking at the differences between temperature distributions in tumours previously irradiated and those not. Another recommended a non-invasive thermometry method that could be further investigated.

Larger studies

Low numbers of patients, inadequate control groups, various treatment parameters and a lack of homogeneity in patient selection criteria have led to criticism in many of the published studies. Prospective, randomised trials should give information as to which patients will benefit from HT and address its future potential in the treatment of advanced breast cancer.

Many patients in the published reports also received adjuvant therapies such as hormone therapy and CH, therefore, how do we know that it is the HT giving the extra benefit? For locally advanced breast cancer RT/HT are rarely used alone in reality. Systemic treatment arms and a control group should be included in trials and not all applied multivariate analysis.[3,13,18]

A large study with positive results may also improve public awareness of HT, thus increasing acceptance of the modality as a viable treatment technique.

Optimum HT/RT regimes

The literature does not conclude an optimum HT regime in terms of temperature, number of treatments or concurrent RT dose. Heating techniques also vary and, to lower the incidence of blistering, radiative techniques and temperature mapping should be used in further trials. Consideration should also be given to the effect of blisters should any of the above variables need increasing.

Triple modality studies

Most studies compare only RT/HT although CH has shown some positive effects and is worth further investigation. The thermal dose relationship for thermoradiotherapy and thermochemoradiotherapy may be different and with a range of CH drugs used in breast cancer the optimum regime is still unknown.

CONCLUSION

The effect of HT in advanced breast cancer is complex, but compared with RT alone HT/RT can improve LC rates in patients with recurrent breast cancer and significantly decrease the risk of local failure. This is particularly relevant for patients who previously received a radical dose of RT to the breast. There is no evidence, however, that HT positively affects overall survival.

Despite previous problems of patient compliance with HT, some newer heating devices have shown major decreases in toxicity and future investigation may further decrease discomfort and blistering. This issue is not significant, however, compared with the effects of uncontrolled local disease and HT ultimately leads to excellent pain control.

Improvements are still necessary for HT in breast cancer treatment before it can be of widespread use. Many papers have shown it to be potentially beneficial, justifying the need for standardising methods, technological development and temperature mapping for future progress and improved clinical results. Non-invasive heating methods may also allow for ease of use.

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APPENDIX 1

Nineteen recent papers on HT were included, of these four are RCT studies, and three are phase 1 or 2 studies. All the papers considered HT and RT in combination and two included the use of chemotherapy.

Only articles that were related to breast cancer and trials published in the last 10 years were selected for review. Others were considered with an emphasis on patient compliance or side effects of HT. Older studies were excluded due to rapid technological advances in RT technique and fractionation, thus questioning their clinical relevance today. Articles relating to whole body or regional HT and other malignancies were also excluded.

Keywords used were hyperthermia, hypoxia, breast cancer, thermoradiation, side effects and compliance.

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