Hyperthermia in Breast-, Bladder-, Cervix carcinoma and Soft tissue sarcoma patients

Project report

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Inhalt

Summary

Objective: to synthesize the evidence on efficacy of hyperthermia in combination with radio- or chemotherapy in breast-, bladder-, cervix carcinoma and soft tissue sarcoma patients.

efficacy analysis

Methods: based on 2 previous systematic reviews a systematic literature search in 4 databases with identical search terms was carried out in order to find randomized clinical trials.

systematic review

Results: 2 RCTs for breast cancer, 2 RCTs for bladder cancer, 3 RCTs for cervix carcinoma, 1 RCT for bladder and cervix and 1 RCT for soft tissue sarcoma were found. Overall, of the 1265 patients 656 were allocated to receive treatment with hyperthermia in combination with radio- or chemotherapy. Where CR or PR was assessed (in 6 from 9 trials) hyperthermia showed statistical significant outcomes. Some of the trials assessed DFS (3/9) or PFS (2/9): all of them show superiority of the hyperthermia arm. Of the 9 publications providing OS data only 1 shows a statistical significant improvement in overall survival, thus proposing that the surrogate endpoints do not translate into a survival benefit and hyperthermia leads to temporal effects only. QoL was not assessed in any of the trials. The reporting of safety data was consistent across the studies showing a trend towards an inferior safety profile within the hyperthermia arms.

9 RCTs for 4 indications:
656 patients in hyperthermia arms

stat. significant outcomes in surrogate endpoints
in 8 of 9 trials: no difference in OS

Conclusion: Due to heterogeneity of the trials in technique, protocol, reporting of outcomes, control interventions, but also tumour characteristics within the same indication there is a high degree of uncertainty and the available evidence must be considered as insufficient. Large confirmatory RCTs are required.

heterogeneity of trials

high degree of uncertainty

Zusammenfassung

Ziel der Arbeit: Synthese der Evidenz zur Wirksamkeit von Hyperthermie in Kombination mit Radio- oder Chemotherapie bei Brust-, Blasen, Zervixkarzinomen und Weichteilsarkomen.

Synthese der Evidenz zur Wirksamkeit

Methode: basierend auf 2 früheren systematischen Reviews wurde eine systematische Literatursuche in 4 Datenbanken mit identen Suchtermini durchgeführt, um randomisierte kontrollierte klinische Studien zu identifizieren.

systematischer Review

Results: Es konnten 2 RCTs für Brustkrebs, 2 RCTs für Blasenkrebs, 3 RCTs für Zervixkarzinom, 1 RCT für Blasen- und Zervixkarzinom and 1 RCT für Weichteilsarkome gefunden werden. Von den insgesamt 1265 Patienten wurden 656 mit Hyperthermie in Kombination mit Radio- oder Chemotherapie behandelt. Wo CR oder PR evaluiert wurde (in 6 von 9 RCTs), zeigte Hyperthermie statistisch signifikant bessere Ergebnisse. Auch in jenen Studien, in denen DFS (3/9) oder PFS (2/9) ausgewertet wurde, wurde eine Superiorität im Hyperthermie-Arm belegt. Von den 9 Publikationen, die Daten zum Überleben/OS präsentieren, zeigte nur 1 eine statistisch signifikante Verbesserung im OS, wodurch geschlossen werden kann, dass die Effekte der Hyperthermie nur temporal sind, da die Surrogatendpunkte nicht durch Gesamtüberleben validiert werden. QoL wurde in keener Studie erhoben. Die Auswertungen zu Nebenwirkungen sind konsistent und zeigen einen Trend zur Inferiorität im Hyperthermie-Arm.

9 RCTs für 4 Indikationen:

656 Pts mit Hyperthermie

stat. signifikant Ergebnisse bei Surrogat-Endpunkten

in 8 von 9 RCTS: kein Unterschied bei Überleben

Conclusion: Aufgrund der Heterogeneität der RCTs bei Technik, Protokoll, Berichterstattung der Endpunkte, Kontrollinterventionen, aber auch bei Tumorcharakteristika innerhalb derselben Indikation besteht ein hohes Ausmaß an Unsicherheit und die Evidenz zur Hyperthermie in den 4 Indikationen muss als insuffizient bezeichnet werden. Große RCTs sind zur Überprüfung der Wirksamkeit notwendig.

Heterogeneität in RCTs

hohes Ausmaß an Unsicherheit zur Wirksamkeit

1 Introduction

Hyperthermia = on the horizon for several decades

Hyperthermia treatment, meaning an intended temperature increase in target tissue to levels above normal systemic temperature, has been looming on the horizon of the highly dynamic field of clinical oncology for several decades now, however without entering the domain of generally accepted treatment modalities. Hyperthermia treatment can be described and classified along a variety of characteristics that are presented below. For a more extensive review of technical, methodological and bio-physical aspects, the interested reader is referred to secondary literature on hyperthermia [1-3].

local, regional & whole-body hyperthermia

invasive & non-invasive methods

Depending on the anatomical extensiveness of the treated area, local, regional and whole-body hyperthermia can be distinguished. The respective methods used for hyperthermia application are to some degree determined by this distinction. In local hyperthermia treatment, non-invasive external approaches to heat up superficial tumors as well as intraluminal and invasive interstitial methods for non-superficial tumors are employed to heat up a well-defined tissue volume. Regional and part-body hyperthermia aims at larger body parts such as affected limbs or organs and relies on non-invasive approaches (i.e. deep tissue hyperthermia) or perfusion with extracorporally heated blood or drugs. For the application of whole-body hyperthermia therapy several methods have been reported, all of them non-specifically raising the temperature of the patient's body while at the same time limiting heat loss.

variety of medical devices: hyperthermia applicator systems

Furthermore, hyperthermia applicator systems rely on different energy sources, such as microwaves, radiofrequency and ultrasound but also simple radiation, all providing the intended heating effect. A variety of applicator systems from different manufacturers have been tested in the clinical setting for this purpose. Injecting magnetic nanoparticles in the treatment area and the subsequent generation of heat by exposing them to external alternating current magnetic fields has been described as a relatively new method of hyperthermia treatment [4].

fundamental therapeutic principle: temperature increase in target tissue

differences in protocols: thermal dosing

duration

number & frequency of sessions

Irrespective of the variety of medical devices and techniques used and the non-uniform heating effects they exert on different anatomical structures exposed, it is important to place emphasis on the mere rise of tissue temperature as fundamental therapeutic principle of hyperthermia treatment and common denominator of the different heating methods. The importance of comprehensive thermometry in target sites as means of documentation of effective heating has consequently been acknowledged by the scientific community and several temperature- and exposure duration-related parameters of possible relevance to hyperthermia efficacy can, in principle, be identified. These include the temporal relationship between primary therapy and hyperthermia as an adjunct, the overall duration of hyperthermia protocols, the number and frequency of hyperthermia sessions, and a number of thermometry-derived measures of presumably effective thermal dosing (i.e. minimum, maximum and average temperature reached, cumulative exposure reached at different threshold percentages of temperature monitoring points). Quality assurance guidelines for several hyperthermia modalities have been developed by expert panels, addressing many of these protocol issues [5-7].

vast majority of clinical evidence on adjuvant hyperthermia

in addition to chemo- or radiotherapy

in a broad variety of tumor populations

effect of adjuvant hyperthermia in cancer treatment still remains to be sufficiently answered

With the focus on cancer treatment as main field of hyperthermia application, a distinction can be made between adjuvant and curative hyperthermia protocols. The vast majority of clinical evidence has been provided for the former, investigating the efficacy of hyperthermia administered in addition to either chemo- or radiotherapy in a broad variety of tumor populations. Regarding the underlying rationale for hyperthermia efficacy and its putative mechanism of action in tumor treatment a number of explanatory hypotheses have been formulated. Besides the rather straightforward cytotoxic effect of excess heat, a synergistic effect of combining radio- or chemotherapy with hyperthermia (also referred to as thermal radio- and chemosensitization) has long been promulgated. Hyperthermia-induced changes to tumor blood circulation (followed by focal metabolic and oxygenation changes), alterations of (sub-)cellular structures, effects on cell metabolism and division, on macromolecule synthesis and DNA repair, but also the impact of hyperthermia on gene expression have been discussed as possible explanations for a more than additive effect of combining hyperthermia treatment with conventional, established radio- or chemotherapy regimens [1-3]. However, the question, if and to what degree (combinations of) the described mechanisms indeed act as primary mediators of an effect of adjuvant hyperthermia in cancer treatment still remains to be sufficiently answered.

debate about therapeutic value in oncology

promising results, but hyperthermia have not found widespread application

Over the last decades, experimental and clinical data on hyperthermia treatment have been generated in a number of preclinical and clinical settings. In light of the already long-lasting hyperthermia technology and protocol development and the still ongoing scientific debate about its therapeutic value in oncology, it has to be noted that while the efficacy and safety of hyperthermia treatment as an adjunct has been investigated in a broad variety of tumor entities and subpopulations where chemo- and/or radiotherapy are or were considered standard of care (with or without surgery), the number of randomized controlled human cancer trials conducted in order to investigate hyperthermia devices appears modest. Given the steady evolution of trial quality and reporting standards over time, the scarcity of recent RCTs is of particular concern. Moreover, in comparison to other pharmacologic and non-pharmacologic trials, most published hyperthermia RCTs have important limitations regarding the size of their respective study populations and varying results were reported for relevant tumor outcomes within and, of lesser significance, across different cancer types. This might serve as explanation why hyperthermia devices, even though some promising results have been published for certain malignancies, have not found widespread application in clinical oncology to this moment.

Purpose for update: 2005 G-BA report on 11 oncologic indications

2010 LBI-HTA report based on G-BA

on the same indications

Purpose: In a rigorous attempt to get hold of the clinical value of hyperthermia in cancer treatment, in 2005 the G-BA (German Federal Joint Committee) published an 870 page systematic review on 11 oncologic indications (processing more than 1.000 citations), concluding that there is insufficient evidence of effectiveness in any of the investigated indications [8]. Hyperthermia was withdrawn from the German service benefit catalogue as a consequence. In 2010 the LBI-HTA (Ludwig Boltzmann Institute for HTA) published a systematic review based on the G-BA report, updating it, and confirming the previous result [9]. The application of hyperthermia treatment in cancer was found to lack the evidence base to be employed outside a clinical trial setting. 53 new citations including 6 controlled clinical studies that were published between 2005 and 2010 were processed for this purpose [9].

2012 LBI-HTA is criticized by Atzelsberg Circle/ hyperthermia providers

In 2012 the Atzelsberg Circle, a German working group consisting of hyperthermia providers, criticized the LBI-HTA for the approach of building on the findings of the G-BA report and for not considering the published trials before 2005 again [10-12]. In an era of ever increasing original/primary medical research, and a growing body of of secondary analyses/systematic reviews, the building of one's own evidence synthesis upon existent high quality reviews with an identical research question is a common and methodically accepted practice among HTA-, EbM- and health care regulatory institutions. Nevertheless, it was decided that a new systematic review on the four indications in question (breast, bladder, uterine cervix cancer and soft tissue sarcoma) [10] would be carried out.

consequently: updated review on breast, bladder and uterine cervix carcinoma and soft tissue sarcoma

Consequently, for the present work we performed a systematic review of randomized controlled trials, comparing hyperthermia treatment as an adjuvant to radio- and/or chemotherapy with radio- and/or chemotherapy alone in the treatment of breast, bladder and uterine cervix carcinoma and soft tissue sarcoma.

effect-centered (not technology-centered) focus on hyperthermia

The approach chosen is effect-centered, meaning that the focus lies on evaluating the efficacy and safety of an intended increase of tumor temperature as an adjuvant in cancer treatment. This approach is believed to follow the proposed rationale for the use of hyperthermia treatment (that is, the radio- and chemosensitizing effect of heating up tumor tissue) in the best possible way. The impact, the choice of a specific heating technology, method or product, might have, is not within the primary scope of this review. Possible weaknesses of such an approach are evident and warrant further consideration later on.

2 Methods

Literature search

based on 2 previous searches, new search in 4 databases 2010-12

A literature search in 4 databases (Medline, EmBase, Cochrane, HTA-Db) was executed in April 2012, delivering 358 citations. The main search tags or MeSH terms used were similar to those employed in the searches of G-BA and LBI-HTA 2010 [8,9]. No additional articles were identified by hand searching the reference lists of available secondary literature on hyperthermia treatment.

pre-defined selection criteria: only RCTs

Along pre-defined criteria (i.e. RCTs comparing radio- and/or chemotherapy plus hyperthermia treatment with radio- and/or chemotherapy alone, reporting efficacy data clearly attributable to any of the four specific cancer populations mentioned above) finally nine original articles (plus two long-term follow-up reports) were included and data were extracted on patient-relevant efficacy endpoints and safety. No further requirements with regards to baseline cancer staging/grading, radio-/chemotherapy or hyperthermia protocol applied, study size, study duration, and the reporting of certain efficacy or safety outcomes were specified. All work steps were carried out and controlled independently by two researchers.

2 RCTs with mixed populations

2 publications with combined results

It should be noted that two of the included studies, (Perez 1991) [13] and (Van der Zee 2000) [14] investigated hyperthermia in mixed cancer populations. However, their reporting allowed for extraction of (at least some) specific outcome data for the individual indications of interest in this review. Furthermore, it has to be pointed out that the publications of (Vernon 1996) [15] and (Van der Zee 2000) provide combined results of five and two independently planned and conducted RCTs, respectively.

Outcomes

intermediate endpoints (surrogates) and final patient-relevant endpoints

methods-guidance by EMA & FDA for evaluation of anticancer medicinal products

The selection of the most relevant endpoints in cancer trials can be difficult, mainly because of the severity of the health state concerned and, depending on the respective tumor type and progression, the often limited life expectancy of study participants. As a result, it might in certain cases be indicated to rely on clinical endpoints that are assessable after a short time span and can serve as intermediates (so called surrogate endpoints). Regulatory bodies such as the U.S. Food and Drug Association (FDA) and the EMA (European Medicines Agency) are constantly concerned with the relevance of specific trial outcomes for market authorization decisions. Therefore, in absence of methodological guidance for medical devices, recommendations made in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [16] and the EMA (Draft) Guideline on the Evaluation of Anticancer Medicinal Products in Man [17,18] were relied on for the selection (and definition) of commonly used cancer outcomes in this review.

endpoints: OS, HRQL

DFS, PFS, ORR

Overall survival (OS) was selected as the main endpoint. It can relatively easily be obtained, is not subject to assessment bias and an undisputed measure of benefit for the patient. Furthermore, endpoints requiring an (additional) assessment of tumor response/status, i.e. disease-free survival (DFS), objective response rate (ORR, taking into account complete and partial re-

sponse), and progression-free survival (PFS), as well as health related quality of life (HRQL) were selected as relevant outcomes.

adverse events: CTCAE criteria

For safety assessment, the Common Terminology Criteria for Adverse Events (CTCAE) version 4 issued by the U.S. NIH/NCI [19] was used as an orientation guide to categorize adverse events into "minor" (CTCAE grade 1-2) and "major" (CTCAE grade 3-4) events. Procedure-related mortality (CTCAE grade 5) was assessed separately.

further intermediate endpoints

RLC, LREC

For an objective assessment of a medical technology it was considered appropriate to focus on a few established clinical endpoints as delineated above. In the present context however, it has to be noted that several of the RCTs reviewed, report „rate of local tumor control" (RLC) and the closely linked „local recurrence" (LREC) after complete response (CR) at a certain point in time as important outcomes. Since the presence or progression of a tumor at the target site would normally, per definition, be captured within PFS or DFS, it can be expected that the rate of local control will bear some value as a surrogate for PFS and DFS. Therefore, in order to avoid omitting relevant information because of terminological discrepancies between trials, data on local tumor recurrence and rates of local control during follow-up were also considered.

3 Results

Two studies on breast cancer [13,15], two on bladder cancer [20,21] (plus one long-term follow-up article [22]), three on uterine cervix cancer [23-25] (plus one long-term follow-up article [26]), one providing data on bladder and uterine cervix cancer [14] and one study on soft tissue sarcoma [27], all of them published in peer-reviewed journals, were reviewed. Two further RCTs on cervical cancer that were identified in our search were not included: (Chen 1997) [28] is available in Chinese only and was therefore not considered. The article by (Datta 1987) [29] was not retrievable even after repeated inquiry with the authors of a Cochrane review from 2010 [30] who cite it in their work.

breast: 2 RCTs
bladder: 2 RCTs
cervix: 3 RCTs
bladder + cervix: 1 RCT
soft tissue sarcoma: 1 RCT

Overall, 374 breast cancer, 236 bladder cancer, 314 cervical cancer patients and 341 patients suffering from soft tissue sarcoma were included in the selected trials. Of the 1265 patients included across all four indications, 656 were allocated to receive hyperthermia treatment. The characteristics of the individual trials are presented in table 3-1. A high degree of heterogeneity between trials regarding hyperthermia technique, protocols and reporting, control interventions but also of tumor characteristics within the same indication is evident, which will be further addressed in the discussion of results. The results obtained for the aforementioned clinical endpoints, where available, are presented below for each indication separately.

1265 pts in all 9 RCTs

656 pts in hyperthermia arms

high degree of heterogeneity in trials

Table 3-1: Trial characteristics. HT=hyperthermia, CTRL=control, RT=radiotherapy, CHT=chemotherapy, BL=baseline, M=median

Study	Tumor	Staging/ Grading	CTRL	n HT vs. CTRL	HT Type	HT protocol (Target temp./session duration/No. of sessions)	Metastasis at BL (%)	Follow-up (months)
Perez 1991 [13]	Breast	n.i.	RT	35 vs. 33	local	42,5°C/60 min/n.i.	n.i.	12
Vernon 1996 [15]	Breast	differ across substudies, n.i.	RT	171 vs. 135	local	differs between substudies	49 vs. 51 (incl. history of met.)	≥5
Colombo 1996 [20]	Bladder	Ta-T1	CHT	29 vs. 23	local	42,5-46°C/n.i./6-8	n.i.	M: 38 vs. 36
Colombo 2003 [21]	Bladder	Ta-T1	CHT	42 vs. 41	local	42°C/40 min/n.i.	Excl. crit.	24
Van der Zee 2000 [14]	Bladder	T2-T4, No, Mo	RT	52 vs. 49	regional	42°C/60 min/5	2 vs. 0	M: 38 (4-76) cross all indications
Sharma 1989 [23]	Cervix	FIGO II & III	RT	25 vs. 25	local	42-42°C/30 min/12	Excl. crit.	18-23
Van der Zee 2000 [14]	Cervix	FIGO IIB, IIIB, IV	RT	58 vs. 56	locoregional	42°C/60 min/5	n.i.	M: 38 (4-76) across all indications
Harima 2001 [24]	Cervix	FIGO IIIB	RT	20 vs. 20	regional	n.i./60 min/3	n.i.	Mean: 36.3 vs. 25
Vasanthan 2005 [25]	Cervix	FIGO IIB, III, IVA	RT	55 vs. 55	n.i.	differs between study centres	Excl. crit.	15.3
Issels 2010 [27]	Soft Tissue Sarcoma	FNCLCC 2 & 3	CHT + Surgery and/or RT	169 vs. 172	regional	42°C/60 min/8 per cycle (2 cycles)	Excl. crit.	M: 36 vs. 32 Max: 128

3.1 Efficacy

Breast cancer: One study, (Vernon 1996), provides information on OS, showing a slight trend towards inferior results for the adjuvant hyperthermia treatment arms, however without reaching statistical significance. The authors also report a statistically significant superiority in PFS for the hyperthermia arm, however limiting endpoint definition to "local progression-free survival". In the same study, CR was observed at a significantly higher rate in the hyperthermia arms in with no difference observed in (Perez 1991). PR was reported by none of the trials, thus not allowing for a statement on the ORR. DFS and HRQL were also not investigated by any of the two studies.

Breast: 2 RCTs, 364 pts

OS: no difference
L-PFS and CR: superiority of HT
QoL: not investigated

Bladder cancer: OS was not found to be of statistically significant difference between the two treatment arms in (Colombo 1996). This finding was confirmed by long-term follow-up data obtained in the patient cohort originally investigated by (Colombo 2003). The same long-term study was the only one to report on DFS and shows superiority of hyperthermia treatment at five years' and ten years' follow-up. CR was observed at a higher rate by (Colombo 1996) and (Van der Zee 2000) under hyperthermia treatment. The former also reports PR data and a significantly higher ORR in the hyperthermia arm. PFS and HRQL were not investigated by any trial. However, (Colombo 2003) reports a statistically highly significant superiority of hyperthermia in local recurrence-free survival after two years.

bladder: 2 RCTs + + 1 mixed pop CT, 236 pts

OS: no difference
DFS, CR, PR, ORR: superiority of HT
QoL: not investigated

Cervical cancer: The results for OS obtained in the uterine cervix cancer population are mixed. Whereas (Van der Zee 2000) and its long-term update (Franckena 2008) show a statistically significant superiority of adjuvant hyperthermia treatment after 3 and 12 years, respectively, the other three studies did not find significant differences between the treatment arms with regards to OS. DFS and (local) PFS were reported by (Harima 2001) only. A statistically significant superiority of hyperthermia regarding PFS was shown after 3 years. The same could not be shown for DFS, however, the difference between treatment arms not reaching statistical significance. Only (Van der Zee 2000) and (Harima 2001) report data on CR, both of them showing a significantly improved CR rate in the hyperthermia treatment arm. (Harima 2001) is the only study providing an ORR, showing an improved response in the hyperthermia arm without clarifying the statistical significance of this finding, though. (Sharma 1989) and (Franckena 2008) both report statistically significant superiority of hyperthermia regarding the rate of local control at 1.5 and 3/12 years respectively. HRQL was not investigated by any cervical cancer trial.

cervix: 3 RCTs + 1 mixed pop CT, 314 pts

OS: inconsistent
1 RCT + follow-up: sign. difference
3 RCTs: no difference

PFS, CR, ORR, RLC: superiority
DFS: no difference

QoL: not investigated

Soft tissue sarcoma: (Issels 2010) did not observe a difference in OS between the two treatment arms after 2 and 4 years. However, at the same points in time, superiority of hyperthermia in local PFS and DFS was shown. ORR was found in favour of hyperthermia treatment. Due to trial characteristics, namely the administration of an induction cycle of hyperthermia prior to surgery, ORR has limited informative value in this specific case, though. Similar to the other three tumor types HRQL was not investigated in the soft tissue sarcoma study.

soft tissue sarcoma: 1 RCT, 341 pts

OS: no difference
PFS, DFS: superiority
QoL: not investigated

Detailed outcome data are presented in table 3-2.

Table 3-2: Efficacy outcomes, shaded fields indicate a statistically significant difference. OS=overall survival, (L)PFS=(Local) progression-free survival, DFS=disease-free survival, ORR=objective response rate, CR=complete response, RLC=rate of local control, LREC=local recurrence, M=median, "s.s."= stated statistically significant without providing details, "n.s.s."=stated as not statistically significant without providing details

Study	Tumor	OS (%)	(L)PFS	DFS (%)	ORR (%)	CR (%)	RLC (%)	LREC (%)
Perez 1991 [13]	Breast	n.i.	n.i.	n.i.	n.i.	33 vs. 31 "n.s.s."	n.i.	n.i.
Vernon 1996 [15]	Breast	2y: 36 vs. 41 p=n.i.	HR: 0.67 p=0.007	n.i.	n.i.	59 vs. 41 p<0.001	n.i.	17 vs. 31 p=n.i.
Colombo 1996 [20]	Bladder	n.i. p>0.3	n.i.	n.i.	100 vs. 48 p<0.01	66 vs. 22 p=n.i.	n.i.	27 vs. 39 p=n.i.
Colombo 2003 [21]	Bladder	n.i.	n.i.	n.i.	N/A	N/A	n.i.	17 vs. 58 Log-rank: p=0.0002
Colombo 2011 (update) [22]	Bladder	n.i. p=0.558	n.i.	5y: 62 vs. 21 10y: 53 vs. 15 p<0.001	N/A	N/A	n.i.	40 vs. 80 p=n.i.
Van der Zee 2000 [14]	Bladder	3y: 28 vs. 22 p=0.33	n.i.	n.i.	n.i.	73 vs. 51 p=0.01	3y: 42 vs. 33 "n.s.s."	n.i.
Sharma 1989 [23]	Cervix	1.5y: 87 vs. 96 p=n.i.	n.i.	n.i.	n.i.	n.i.	1.5y: 70 vs. 50 "s.s"	30 vs. 50 p=n.i.
Van der Zee 2000 [14]	Cervix	3y: 51 vs. 27 p=0.009	n.i..	n.i.	n.i.	83 vs. 57 p=0.003	3y: 61 vs. 41 p=n.i.	n.i.
Franckena 2008 (update) [26]	Cervix	12y: 37 vs. 20 p=0.03	n.i.	n.i.	N/A	N/A	5y: 61 vs. 37 12y: 56 vs. 37 p=0.01	25 vs. 31 p=n.i.
Harima 2001 [24]	Cervix	3y: 58 vs. 48 p=0.3	3y: 80 vs. 49 p=0.048	3y: 63 vs. 45 p=0.2	95 vs. 75 p=n.i.	80 vs. 50 p=0.048	n.i.	10 vs. 30 p=n.i.
Vasanthan 2005 [25]	Cervix	n.i. p=0.1893	n.i.	n.i.	n.i.	n.i.	3y: n.i. p=0.58	n.i.
Issels 2010 [27]	STS	2y: 78 vs. 72 4y: 59 vs. 57 p=0.43	2y: 76 vs. 61 4y: 66 vs. 55 M: p=0.003	2y: 58 vs. 44 4y: 42 vs. 35 M: p=0.011	29 vs. 13 p=n.i.	3 vs. 1 p=n.i.	n.i.	n.i.

evidence across indications:

OS: 8/9 RCTs no difference

1 RCT: cervix carcinoma

Looking at the evidence across indications, what conclusions that can be drawn for each of the clinical endpoints? For OS a relatively homogeneous picture can be drawn. Including the two long-term follow-up studies, nine publications provide OS data. Among them, only (Van der Zee 2000) and (its update) (Franckena 2008) show a statistically significantly improved OS for its cervical cancer cohort under adjuvant hyperthermia treatment. None of the remaining cervical cancer trials supports this finding. Looking at the other three cancer types, no hyperthermia-related overall survival benefit has been reported for either of them.

surrogate endpoints show superiority of HT

but did not translate into a overall survival benefit

Three articles, (Issels 2010), (Colombo 2011) and (Harima 2001) report DFS data. Of note, all of them show higher DFS rates in the hyperthermia treatment arm, the former two meeting the statistical significance threshold. PFS data was provided by (Vernon 1996), (Issels 2010) and (Harima 2001), all of them showing superiority of hyperthermia. However, all three of them restrict their definition of progression to „local tumor progression". While there is only limited availability of DFS and PFS data compared to OS results, the fact that superiority in (the subordinate survival outcomes) DFS or PFS did in neither case translate into a overall survival benefit, has to be noted.

CR shows most favorable outcome results

but: (confirmative) statistical analysis seldom performed

CR was assessed by six of the original trials. In all cases except for (Perez 1991) and (Issels 2010) was hyperthermia found to improve the rate of CR at a level of statistical significance, thus showing maybe the most favorable outcome pattern among the selected endpoints. PR rates were reported by (Colombo 1996), (Issels 2010) and (Harima 2001), consequently allowing for ORR to be calculated. In line with the results obtained for CR, all three studies showed a higher ORR under hyperthermia treatment, however only (Colombo 1996) having performed a (confirmative) statistical analysis.

Of the studies reporting RLC and/or LREC all but one (Vasanthan 2005) showed results indicative of a beneficial effect of hyperthermia on these parameters. Only three of them provided a confirmative statistical analysis, though.

3.2 Safety

7/9 RCTs safety data:

consistently higher in pts with hyperthermia

Attributable safety data were reported by seven studies in total. Whereas the two mixed population studies (Perez 1991) and (Van der Zee 2000) also provided general safety information, no indication specific data have been reported. Overall complication rates were extractable from six studies and were consistently higher in patients undergoing hyperthermia treatment with the exception of Sharma 1989 who reported radiation-related reactions only. Distinguishing between minor and major AEs, both domains reflect the pattern described for overall complications. Procedure related mortality was reported by (Issels 2010) only. Detailed safety data are presented in table 3-3.

Table 3-3: Safety outcomes. AE=adverse event, HAT=hyperthermia, RT=radiotherapy, CHT=chemotherapy

Study	Tumor	Overall complications (n)	Major AEs (n)	Minor AEs (n)	Procedure related deaths (n)
Perez 1991 [13]	Breast	n.i.	n.i.	n.i.	n.i.
Vernon 1996 [15]	Breast	303 vs. 191	n.i.	n.i.	n.i.
Colombo 1996 [20]	Bladder	n.i.	0 vs. n.i.	"all" vs. "less"	n.i.
Colombo 2003 [21]	Bladder	70 vs. 30	13 vs. 1	57 vs. 29	n.i.
Colombo 2011 (update) [22]	Bladder	n.i.	n.i.	n.i.	n.i.
Van der Zee 2000 [14]	Bladder	n.i.	n.i.	n.i.	n.i.
Sharma 1989 [23]	Cervix	RT related: 25 vs. 25 HT related: n.i.	RT related: 2 vs. 2 HT related: n.i.	RT related: 23 vs. 23 HT related: n.i.	n.i.
Van der Zee 2000 [14]	Cervix	n.i.	n.i.	n.i.	n.i.
Franckena 2008 (update) [26]	Cervix	n.i.	n.i.	n.i.	n.i.
Harima 2001 [24]	Cervix	6 vs. 0	3 vs. 0	3 vs. 0	n.i.
Vasanthan 2005 [25]	Cervix	14 vs. 8	3 vs. 3	11 vs. 5	n.i.
Issels 2010 [27]	STS	CHT related: 220 vs. 186 HT related: 209 vs. N/A	CHT related: 220 vs. 186 HT related: 36 vs. N/A	CHT related: n.i. HT related: 173 vs. N/A	2 vs. 1

4 Discussion

The results obtained for efficacy of hyperthermia treatment as an adjuvant to chemo- and/or radiotherapy are indicative of a relatively consistent trend towards a slight improvement in survival parameters within and across the four investigated indications. However, differences in survival appear to be small and a statistically significant improvement in OS is reported by a single study (and its long-term follow-up) only. It has to be noted in this context, that none of the studies had OS declared the primary outcome parameter. It is therefore possible that the inability to yield statistically significant results in favor of hyperthermia treatment might to some extent be caused by a lack of power.

results:
only 1 in 9 RCTs show stat. significant improvemnet in survival

possibly caused by lack of power of RCTs

More generally, the size of the studies investigated appears very modest with only two of them providing data on substantially more than 100 participants. One of them, (Vernon 1996), actually reports compiled data of five different RCTs. As stated above, these trials were originally initiated independently but merged over time to overcome recruitment problems. The decision to conduct small trials might have been influenced by the comparably business-friendly regulatory framework in place for medical devices, which demands far less data obtained from (randomized) controlled trials for market approval than for pharmaceutical innovations.[31] Nonetheless, the predominance of small study populations hampers the ability to make evidence-based judgments about the clinical performance of hyperthermia as a treatment modality in cancer and is considered a major limitation of the available evidence base on hyperthermia. For this review, it was deliberately decided not to limit inclusion to trials of a certain population size in order to cover the available literature comprehensively. Resulting uncertainty regarding efficacy estimates and the inability of small trials to detect rare but potentially severe safety signals, are important shortcomings, though.

hyperthermia since 20 years:

number of studies: modest &

size of studies small

possible cause: medical device regulation demands less data than for drugs

evidence-based judgments are hampered: major limitation

The majority of studies reporting endpoints that require local tumor assessment (ORR, CR, local PFS, rate of local control and recurrence) show promising results for hyperthermia treatment. Interestingly though, benefit observed at the level of local tumor response does not translate into an improved OS in most of the trials, with (Van der Zee 2000) being the sole exception. This raises the question why and how an apparent initial treatment benefit achieved by hyperthermia administration is offset over time. One possible explanation might be the presence of metastatic disease at baseline, diminishing the impact the investigated and treated target lesion has on overall disease progression and consequently the relevance of any endpoint focusing on exactly this target lesion. Also, it cannot be excluded that hyperthermia itself has some adverse effect on tumor progression outside the treated area. Showing superiority in local tumor response with non-superiority in OS at the same time warrants careful consideration of the possibility of a favorable local response accompanied by inferiority regarding an effect on distant disease manifestation. Another explanation might be that the investigated malignant lesions actually had only little bearing on the survival of the affected patients, implying too few events (i.e. deaths) recorded in the studies. However, taking into account the OS rates, where reported, this appears unlikely.

trials are based on local tumor assessment: promising results

but do not translate into improved OS

open question: presence of metastatic disease elsewhere than treated target or

hyperthermia has AE on progression outside treated target

surrogate vs. patient-relavant endpoints

QoL as patient-relevant endpoint is not evaluated

Regulatory guidelines describe the relevance of different cancer outcomes mainly from the perspective of their surrogate value for the generally preferred OS [16-18]. This is a comprehensible shortcut to showing the relevance of these endpoints to the patient and reflects some of the regulatory difficulties that need to be overcome in drug approval. However, it should be kept in mind that any treatment potentially affects not only the temporal aspect of survival but also quality of life (united in the quality-adjusted life-year (QALY) concept [32]). It is therefore regrettable that none of the identified trials performed HRQL assessment of patients undergoing hyperthermia treatment.

reporting of safety data: very inconsistent

The reporting of safety data was very inconsistent across the reviewed studies. Different grading systems applied for AE classification and differences in follow-up serve as possible explanations. Most importantly, though, considerable discrepancies in overall complication rates between the different studies clearly suggest that the rigor of safety signal recording and/or reporting has not been the same in all of them. Narrative reporting in some cases rendered it difficult or impossible to comprehensively extract safety data. Making a clear-cut statement on the safety of adjuvant hyperthermia based on the available data is considered difficult in light of these limitations. Drawing solely on those trials providing comprehensive safety information, a trend indicating an inferior safety profile of adjuvant hyperthermia can be observed.

sources of bias

trial-design:
no blinding of pts

Apart from the clinical findings, there are several issues relating to trial design and conduct that warrant further discussion due to their possible impact on data quality. First and foremost, none of the reviewed studies was conducted in a blinded, placebo controlled fashion. The mere impossibility of blinding trial participants when investigating certain medical devices is an acknowledged problem [31]. In the present case of hyperthermia devices, it appears that at least in some studies, the inclusion of a sham hyperthermia application procedure in the control arm and thus (participant) blinding might have been technically possible in principle. Of course, the necessary effort and resource use might have been considerable.

no blinding of outcomes assessors

(only in 1 RCT)

no allocation masking

performance or detection bias

That being said, the assessment of outcomes in medical device trials is not by default prone to the same limitations. Even if blinding was not achievable during the treatment period in the case of hyperthermia application, it would have been critical to at least have outcomes that are subject to clinical judgment (i.e. ORR, tumor progression, etc.) assessed by an investigator masked to the prior treatment allocation. Unfortunately, blinded review of tumor response or progression was reported by (Issels 2010) only. (Vernon 1996) describe independent verification of the "majority" of tumor measurements, however it is unclear if this was done with allocation masking. The finding that results obtained for the only "hard" outcome (i.e. OS) did not support the superiority of adjuvant HT therapy over chemo-/radiotherapy alone in most of the studies whereas outcomes with subjective assessment (e.g. CR) did, has to be interpreted carefully in this context. Some degree of performance or detection bias having influenced those study outcomes that are based on tumor assessment cannot be excluded.

This review included four different cancer types treated with a variety of hyperthermia methods and specific devices. Naturally, the fundamental differences in tumor and patient characteristics and the resulting chemo- and radiotherapy regimens must not be overlooked in assessing the clinical value of additional hyperthermia treatment in general. It has to be assumed that the efficacy and toxicity of hyperthermia will not be uniform for different radiation doses or chemotherapeutic agents used as basic therapy. Moreover, there are differences with regards to the hyperthermia protocols set up for each of the included trials (i.e. target temperature, number of hyperthermia sessions, duration of each session). These trials were not conducted as dose-finding studies, and the influence these differences had on the individual studies' outcome is unclear. Compliance with the predefined hyperthermia protocol, where part of the assessment, was not optimal in several trials, (e.g. in (Issels 2010) and (Vernon 1996), unfortunately at the same time comprising the two largest studies). This includes not reaching or not maintaining the intended tumor temperature as measured by thermometry and patients undergoing less than the intended number of hyperthermia sessions. Whether and how this has impacted individual study results is unclear. Whereas efficacy outcomes might have suffered from subpar protocol adherence, premature interruption of hyperthermia treatment might at the same time hint at possible tolerability issues not necessarily represented in the reported safety results. Furthermore, if suboptimal protocol compliance is already considered a matter of criticism in the well-controlled setting of a clinical trial, there has to be even greater concern regarding hyperthermia use in a real-life setting. The question how other anti-cancer therapy was standardized during the study (in particular during long-term follow up) and accounted for in outcome assessment (e.g. by censoring patients who received other treatment) has not been answered by several trials. It cannot be excluded that this had an impact on study outcomes, especially in the smaller trials.

limitations of review:

4 different cancer types

differences in tumor-satges and patient characteristics

in chemo- and radiotherapy regimens

in hyperthermia protocols

compliance with predefined protocol, safety reporting

premature interruption of treatment

etc.

A systematic review and meta analysis of hyperthermia as an adjunct to radiotherapy in the treatment of uterine cervix carcinoma was recently published, looking at the four articles on cervix cancer reviewed in this work plus the articles by (Chen 1997) and (Datta 1987), which could not be considered here, for reasons explained above [30]. Based on a pooled data analysis, hyperthermia as an adjunct to radiotherapy was found superior to radiotherapy alone in the endpoints CR and LREC, as suggested here, but also in OS. Thus, sample size might indeed have had an important limiting factor for showing an overall survival benefit. Similar to the concerns raised here, small trial size, and differences in (hyperthermia) treatment in and between trials have been criticized. Interestingly though, the fact that no study was conducted in a blinded fashion was not considered a relevant source of bias.

recent systematic review & meta analysis of hyperthermia (Cochrane report) included 2 more RCTs:

1 chinese +
1 not available from 1987

difference in OS ?

5 Conclusion

HT: beneficial in intermediate

OS: 8/9 RCTs no difference

small trials: lack of statistical power ?

For the four reviewed indications, hyperthermia application as an adjuvant to a radiotherapy or chemotherapy protocol appears beneficial in terms of intermediate endpoints relying on tumor assessment, such as overall, complete and partial response rates, local control and (local) progression free survival in the majority of studies. Whereas the clinical relevance of tumor response outcomes for the cancer patient will vary with indication, their importance for certain cancer subpopulations is underpinned by a history of successful drug approval procedures relying on such endpoints as primary outcome measures [33]. At the same time, only one single trial, conducted in uterine cervix patients, showed a statistically significant improvement in overall survival. This might be explained by a mere lack of statistical power to detect an overall survival difference but needs further investigation nonetheless. Regarding hyperthermia toxicity it has to be stated that while the informative value of the reported safety data is considered limited for several trials, hyperthermia was found to be associated with an increased frequency of adverse events, both major and minor.

important degree of uncertainty

limited overall number of RCTs

non-blinded

prone to bias

There is an important degree of uncertainty that comes with these results. First and foremost, the majority of the reviewed trials were performed in inappropriately small samples for phase III trials, raising questions about the accuracy of efficacy estimates and the comprehensiveness of the available safety database. Furthermore, due to the limited overall number of RCTs conducted, but also due to differences in trial design, baseline conditions, treatment protocols and endpoint selection between studies on the same indication, most of the positive outcomes obtained have not been replicated and yet remain to be confirmed on a larger scale. Further uncertainty stems from the fact that neither of the trials considered in this work was conducted in a blinded fashion. While this can indeed be considered a device-inherent problem, the resulting risk of investigator related bias could have been mitigated in part by arranging for masked tumor assessment. This, however, was only done in two trials.

insufficient evidence

large confirmatory RCTs necessary

In summary, the available evidence on hyperthermia as an adjuvant to radiotherapy and chemotherapy in the treatment of breast, bladder, uterine cervix carcinoma and soft tissue sarcoma is considered insufficient at the moment to make a clear judgment on its clinical benefit and associated risks. This, together with uncertainties concerning the validity of the currently available data would suggest the conduct of large confirmatory RCTs for each indication, taking on the methodological and protocol-related challenges mentioned above to close the present evidence gap.

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