International Journal of Hyperthermia

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ihyt20

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To cite this article: Paraskevi Danai Veltsista, Eva Oberacker, Adela Ademaj, Stefanie Corradini, Franziska Eckert, Anne Flörcken, David Kaul, Lars H. Lindner, Rolf Issels, Oliver J. Ott, Daniel Pink, Vlatko Potkrajcic, Peter Reichardt, Siyer Roohani, Mateusz Jacek Spalek, Oliver Riesterer, Daniel Zips & Pirus Ghadjar (2023) Hyperthermia in the treatment of high-risk soft tissue sarcomas: a systematic review, International Journal of Hyperthermia, 40:1, 2236337, DOI: 10.1080/02656736.2023.2236337

To link to this article: https://doi.org/10.1080/02656736.2023.2236337

Published online: 19 Jul 2023.

INTERNATIONAL JOURNAL OF HYPERTHERMIA
2023, VOL. 40, NO. 1, 2236337
https://doi.org/10.1080/02656736.2023.2236337

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REVIEW ARTICLE

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Hyperthermia in the treatment of high-risk soft tissue sarcomas: a systematic review

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ABSTRACT

Background: The therapy of high-risk soft tissue sarcomas (STS) remains an interdisciplinary challenge. Regional hyperthermia (RHT) sparked interest as it has been shown to improve overall survival when added to perioperative chemotherapy (CTX). However, questions arise on how RHT should be optimally integrated into current multi-modal therapies.

Materials and Methods: We performed a systematic literature review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies written in English and focused mainly on radiative RHT and superficial hyperthermia were evaluated and included. Studies including patients below the age of 18, with metastatic disease or review articles, were excluded.

Results: We identified 15 clinical reports from 1990 until July 2022. Three articles combined RHT + CTX, and twelve focused on combined RHT + radiotherapy (RT) or neoadjuvant chemoradiotherapy (CRT). Most treatments were based on invasive thermometry, and less on magnetic resonance imaging (MRI)-based, noninvasive thermometry for STS of the extremities. Perioperative chemotherapy was used for the combination of RHT and CTX, mostly Ifosfamide-based. The effectiveness of RT appeared to be increased by RHT, especially with two RHT sessions/week. The trimodal simultaneous approach of neoadjuvant RHT and CRT was also feasible. No significant toxicity of RHT was reported.

Conclusions: The gathered data strengthen the beneficial role of RHT in the multimodal setting. Further expert consensus and clinical trials are required to determine the optimal integration of RHT in treating STS.

ARTICLE HISTORY
Received 8 June 2023
Revised 7 July 2023
Accepted 7 July 2023

KEYWORDS
Hyperthermia; sarcoma; high-risk; radiation; chemotherapy

1. Introduction

Patients bearing high-risk soft-tissue sarcomas (STS, >5 cm in size, deep location with grade 2-3 according to the Fédération Nationale des Centers de Lutte Contre le Cancer – FNCLCC) have an unfavorable prognosis, with approximately 50% of the patients dying within 5 years of diagnosis despite multimodal treatment approaches. Complete tumor resection remains essential to achieving a cure for the disease [1]. For sarcomas of the extremities and the superficial trunk wall, local control can be improved by the addition of neoadjuvant- or adjuvant radiotherapy (RT) [2,3]. The question of whether the use of neoadjuvant or adjuvant RT is preferred is still under debate, although the notion is moving toward neoadjuvant RT due to a favorable toxicity profile and similar oncological outcomes [4–6]. A recent multi-center, open-label, randomized, phase III trial (European Organization for Research and Treatment of Cancer - EORTC- 62092: STRASS) [7] evaluated the addition of neoadjuvant RT of 50.4 Gy for retroperitoneal sarcomas. The authors showed elevated toxicity and no improvement in outcome and concluded neoadjuvant RT to be a debatable approach for treating

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retroperitoneal sarcomas. Nevertheless, in the STREXIT study on liposarcomas (which constitute the most common subcategory of retroperitoneal sarcomas) [8] neoadjuvant RT was associated with enhanced abdominal-recurrence-free survival (ARFS) in patients with primary, well-differentiated liposarcoma (HR, 0.61; 95% CI, 0.42–0.89) as well as in patients bearing dedifferentiated liposarcoma grade 1 or 2 (HR, 0.63; 95% CI, 0.40–0.97).

Other studies have raised the question of whether doxorubicin-based chemotherapy (CTX) can improve outcomes in STS patients. In 2001 a phase II clinical trial by the EORTC, randomized 134 patients into two groups: one receiving 3 cycles of neoadjuvant CT (ifosfamide and doxorubicin) before surgery vs surgery alone. The trial outcome was essentially negative, since the percentage of disease-free patients at 5 years was similar in both arms (52% in the surgery alone arm and 56% in the neoadjuvant arm). This is hypothesizing that >3 cycles of CTX are required [9]. Subsequently, several other randomized trials were conducted but the results remained conflicting, and the role of CTX for STS remains vague [10]. In cases of retroperitoneal STS, two significant studies [11,12], established that neoadjuvant and perioperative systemic CTX, do not improve the survival of the patients. The results of a randomized trial from four international centers [13,14] indicated that anthracycline-based neoadjuvant CTX (epirubicin & ifosfamide) should remain the regimen of choice for high-risk STS whenever neoadjuvant CTX is administered, as it led to a 10% improvement in 5-year OS compared to histology-tailored CTX for high-grade myxoid liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor and, undifferentiated pleomorphic sarcoma (trabectedin; gemcitabine/dacarbazine; ifosfamide; etoposide/ifosfamide; and gemcitabine/docetaxel respectively).

However, in the retrospective EORTC study of D' Ambrosio [15], which constitutes the largest retrospective study for leiomyosarcomas, the combination of doxorubicin and dacarbazine was preferred. CTX with doxorubicin was compared to doxorubicin combined with ifosfamide in unresectable or metastatic STS patients in the phase III randomized controlled trial EORTC 62012 [16]. The trial results indicated that the response rate and progression-free survival (PFS) were increased after the CTX combination, but this was associated with higher grade 3-4 toxicities. The authors therefore concluded that intensified CTX is less suitable for palliation but might be justified when the therapy goal is tumor shrinkage.

High morbidity and mortality of the localized STS as well as the common occurrence of distant metastatic disease which can be partially influenced by current chemotherapeutic regimens but not by RT application, remain unsolved clinical problems in patients with STS. This indicates the emerging need for a more efficient, multimodal approach that will contribute to the local control of the tumor as well as to the control of the distant metastatic disease, improving patients overall survival (OS) and quality of life. The implementation of radiative regional hyperthermia (RHT) using a radiofrequency annular-phased-array-based heating approach to improve RT and/or CTX of RHT has been investigated through clinical trials since 1986. RHT increases the tumor temperature to 39.5–43°C in the abdominopelvic region and the extremities and it has been described to improve the effectiveness of RT and/or CTX without adding significant toxicity [17].

The investigation of the RHT integration in the STS therapies led to therapeutic protocols including RHT into chemotherapeutic schemes through two prospective precursor clinical trials conducted in the Ludwig Maximilian University of Munich (RHT-91 [18], RHT-95 [19]) and a confirming multicentric international randomized controlled trial EORTC 62961/ESHO RHT-95 [20]. RHT-91 and RHT-95 were the initial phase II trials that investigated the combination of the etoposide, ifosfamide, doxorubicin (EIA) regimen with RHT. The therapeutic strategy was the same in both studies, except in the RHT-95 trial, the patients received EIA alone after surgery, unlike RHT-91 where patients also received adjuvant RHT if feasible. The EORTC 62961/ESHO RHT-95 clinical trial was an open-label, phase III randomized clinical trial that evaluated the efficacy and toxic effects of perioperative EIA CTX (4 neoadjuvant and 4 adjuvant cycles) plus RHT in 341 adult patients with localized, high-risk STS. The results demonstrated improved local progression-free survival (LPFS) and significantly prolonged 5-year and 10-year OS rates in favor of RHT. These data were acknowledged by German national and European international guidelines for sarcoma therapy and in Germany; certified sarcoma centers are now required to provide access to an RHT facility [21].

This resulted in increased interest regarding RHT. However, in many sarcoma centers with different institutional multimodal therapy approaches for STS, the question of how to optimally integrate RHT in today's clinical practice arises. These questions include medical issues such as the choice of CTX drugs and the number of cycles required as well as potential benefits of trimodal neoadjuvant CRT combined with RHT and technical issues such as the conduction of thermometry, among others. The above-mentioned inquiries formed the core objective of this systematic literature review which is to analyze the literature on therapeutic patterns that will help us to facilitate the integration of RHT in the therapeutic strategies against STS.

2. Materials & methods

Only studies that were published between 1990 and July 2022 and were written in English were evaluated during the literature research. Studies on patients below 18 years of age or/and patients with metastatic disease and review articles were excluded. PubMed was the primary source for our research, and the personal archive, as well as the sources referred to therein, constituted supplementary sources of publications.

The final fifteen studies selected in the current review focus mainly on radiative annular- phased-array-based RHT as part of the sarcoma therapeutic scheme. Some articles used superficial HT (SHT) in a fraction of patients and one applied capacitive HT in a subset. Other articles focusing solely on different treatment modalities, such as whole-body HT, capacitive HT, thermo-ablation, or isolated hyperthermic limb perfusion, were excluded. Table 1 presents the principal

Table 1. Terms of literature research on PubMed.

Literature research term	
Search terms	No. of results per search
(Sarcoma) AND ((Hyperthermia) OR (hyperthermic) OR (Thermotherapy) OR (Thermal therapy) OR (thermometry))	121
(sarcoma) AND ("hyperthermia"[All Fields])	110
(sarcoma) AND (thermotherapy)	99
(sarcoma) AND (hyperthermic therapy)	48
(sarcoma) AND ((radiation) AND (hyperthermia))	39

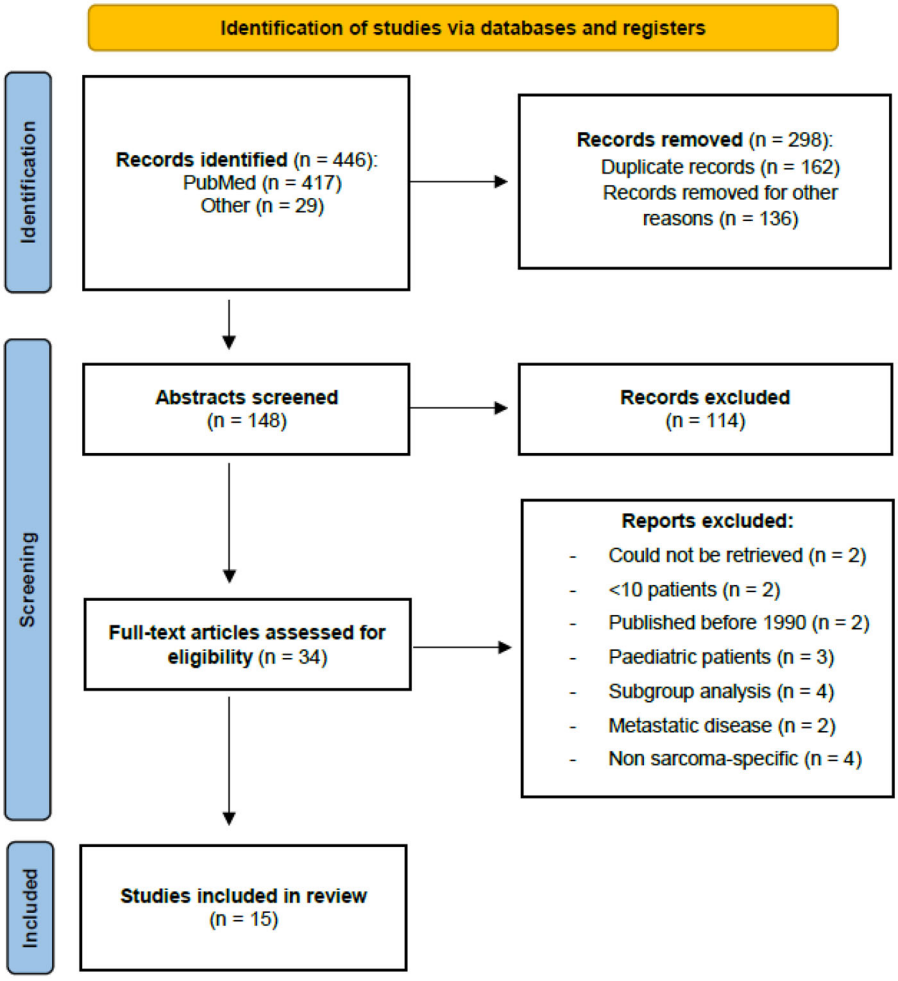

Figure 1. Flow diagram of the literature research according to PRISMA guidelines [22].

terms used for the PubMed search. The above search terms led to the retrieval of 446 papers *via* PubMed, personal archive and the sources referred to therein, which were assessed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22] guidelines, as it is shown in Figure 1, and the PRISMA checklist [23]. The final fifteen manuscripts were thoroughly evaluated and included in the current study.

3. Results

A total of 15 studies were selected. RHT was combined with CTX in 3 studies (Table 2) with sequential application of RT if indicated and in 12 trials (Table 3), RHT was combined with RT or CRT with sequential further CTX if indicated.

3.1. RHT combined with CTX

In 2001, Issels et al. published the results of the RHT-91 protocol application on 59 STS patients. Patients with persistent or recurrent high-risk STS after previous attempts of resection with or without radiotherapy were eligible. RHT was administered in a neoadjuvant manner combined with 4 cycles of EIA CTX in 59 patients. Only patients with a grade II and III STS, Karnofsky performance status of $\geq$60% and no evidence of distant disease could participate in the trial. The thermometry protocol was previously published [37]. Specifically, catheters were placed either with x-ray guidance (percutaneously) or under computed tomography guidance during laparotomy. In both cases, catheters were placed intratumorally, and the time-averaged thermal parameters of T_{90}, T_{50}, T_{20}, T_{min} and T_{max} (temperature achieved in 90%,

Table 2. Trials that are included in the current review that have employed RHT and CTX or CRT.

RHT and CTX/CRT								
First author	Trial Design	N	CTX/CRT	RHT	Surgery	Thermometry	Efficacy	Toxicity
Issels et al. 2001 [18]	Prospective, single-arm	59	4× EIA (+ adj. 4 × EIA in case of progression)	2 × RHT/3 weeks (8 × RHT in total), 1 h (2 × RHT/4 weeks, 16 × RHT in total in case of progression)	Week 14 (If indicated)	Invasive thermometry	Pathological response, LFFS, DMFS, EFS, OS	WHO criteria
Wendtner et al. 2001 [19]	Prospective, single-arm	54	4× EIA + 55– 65 Gy (1.8– 2.0 Gy)	2 × RHT/3 weeks (8 × RHT in total), 1 h	Week 14 (If indicated)	Invasive thermometry	LFFS, DMFS, EFS, OS	CTC
Issels et al. 2010 [24] 2018 [20]	Prospective, randomized, multicenter	341/ 332	4× EIA + 50.0- 60.0 Gy (1.8- 2.2 Gy/day) + 66.0 Gy Boost (+ adj. 4 × EIA post-induction)	2 × RHT/3 weeks induction + 2 × RHT/ 3 weeks post-induction (16 × RHT in total), 1 h	4-6 weeks post-induction therapy	Invasive thermometry	LPFS, DFS, OS	CTC

CTC: Common Toxicity Criteria; CRT: Chemoradiotherapy; DFS: Disease-Free Survival; DMFS: Distant Metastasis-Free Survival; EFS: Event-Free Survival; EIA: Etoposide; Ifosfamide; Doxorubicin; LFFS: Local Failure-Free Survival; LPFS: Local Progression-Free Survival; OS: Overall Survival; RHT: Regional Hyperthermia; WHO: World Health Organization.

50%, and 20% of the target volume and minimum/maximum temperature achieved in target volume, respectively) were evaluated. RHT was applied using the BSD 2000 system. The treatment objective was attaining a $T_{max} \geq 42\,^{\circ}C$. The authors report that the treatment objective of adequate hyperthermia in deep-seated, large STS could be achieved in all patients. Postoperatively, patients with signs of response and without progressive disease received 4 cycles of etoposide and ifosfamide combined with RHT. Patients not previously treated with RT and exhibiting positive surgical margins or residual disease were treated with RT alone for a total dose of around 55-65 Gy (daily fractions of 1.8–2 Gy). The median follow-up time for the 59 patients was 82 months, and it revealed that the OS rates were significantly different depending on the response or the absence of it. Specifically, patients who had presented pathological and clinical responses toward neoadjuvant therapy reached 54% of survival within 108 months, compared to 20% for the non-responders, while extremity and non-extremity sarcomas did not present any statistically significant difference.

Wendtner et al. published the results of the RHT-95 prospective study in 2001. In this trial, 54 patients with high-risk STS (≥5 cm, Grade II and III) were treated with neoadjuvant and adjuvant schemes incorporating RT, RHT and CTX. In the neoadjuvant setting, CTX and RHT were employed. The CTX scheme comprising EIA and RHT was repeated every three weeks for a total of four courses, using the BSD 2000 system and reporting T_{min}, T_{max}, T_{90}, T_{50} and T_{20}. For the patients who did not exhibit progressive disease after the neoadjuvant schemes, resections (where applicable) and four cycles of EIA were applied. For patients without prior RT, adjuvant RT of a total dose of 55-65 Gy in daily fractions of 1.8- 2 Gy, was applied. Comparing the presented study (only neoadjuvant RHT + CTX) to the foregoing RHT-91 trial (neoadjuvant and adjuvant RHT + CTX), a 4-year follow-up in the RHT-95 trial exhibited inferior local failure-free survival LFFS ($p = 0.027$) rate, which was not reflected in distant metastasis-free survival (DMFS) or OS ($p = 0.558$ and $p = 0.126$ respectively), underlining that RHT + CTX is important for local tumor control without, however, affecting the OS. The thermometry followed the same protocol as reported for the RHT-91 trial [37].

In 2010, Issels et al. assessed the safety and the efficacy of RHT combined with neoadjuvant and adjuvant CTX (EIA) in the context of the largest, randomized phase III trial employing neoadjuvant CTX for high-risk STS. Three hundred forty-one patients, ≥18 years of age, bearing STS of grade 2 or 3 (FNCLCC risk criteria) deep to the fascia and with a tumor diameter of 5 cm or more with no evidence of distant metastases were eligible for the trial. Patients were randomly assigned to the control (EIA alone) or the experimental (EIA + RHT) arm for 4 cycles of treatment before the response assessment and the resection. For the application of RHT, the BSD 2000 system was used. Ifosfamide was applied simultaneously during the RHT session. After the resection, in patients where radiotherapy was indicated (62 and 64% of the patients from the EIA alone and EIA + RHT group respectively), a total dose of 50–60 Gy was delivered

Table 3. Trials that are included in the current review that have employed RHT and RT.

RHT and RT

First author	Trial Design	N	RT	RHT	Surgery	Thermometry	Efficacy	Toxicity
Leopold et al. 1992 [25]	Prospective, randomized	44/45	50 Gy (1.8–2 Gy/fr.) adj. Dx–based CTX to 4/44 p.	<1h Post-RT, 1 × RHT/week vs 2 × RHT/week for 1 h (5 vs. 10 × RHT in total)	≈4–6 weeks post-RHT/RT	Invasive thermometry	> 80% Necrosis	Mild, moderate, severe
Prosnitz et al. 1999 [26]	Prospective, single-arm	97	50 Gy (1.8–2 Gy/fr.), adj. Dx–based CTX to 8/97 p.	< 1h post-RT, 1xRHT/week or 2xRHT/week for 1 h	4–6 weeks post-RHT/RT	Intratumoral thermometry	RFS,CSS, OS, LC	n.a.
Maguire et al. 2001 [27]	Prospective, single-arm	35	50 Gy (1.8–2 Gy/fr.), ×5/week	2 × RHT/week, 1-2 h	5–6 Weeks post-RT	Invasive and oral ther mometry	pCR, LC, DM	RTOG
Dewhirst et al. 2005 [28]	Prospective, single-arm	35	50 Gy (1.8– 2 Gy/fr.), ≥ 4 MV external beam	<1h Post-RT, ×2/week	4–6 Weeks post-RT	Multipoint invasive ther- mometry	pCR, MFS, OS	n.a.
de Jong et al. 2012 [29]	Retrospective	16	32–36 Gy (3– 4 Gy/fr.), 6 Gy for 1p., 15 Gy (2.5 Gy/fr.) for 1p.	2 × SHT/week, 1h	Prior RT/RHT	Superficial thermometry	RECIST	n.a.
Linthorst et al. 2013 [30]	Retrospective	24	32–54 Gy (2–5 Gy/fr)	Post RT 3–6 cycles 1 × SHT or 2 × SHT/week 1h	For 11/24 patients, pre- and post-operative RT applied	Interstitial and/or su perficial thermometry	DLC, OS	CTCAE v.3.0
Eckert et al. 2013 [31]	Retrospective	28	45 Gy (44–56 Gy) and Ifosfamide (d. 1––5 or d1 + d2) neoadj.	1–2 RHT/week	post-RT and multimodal therapy	n.a.	LC, DFS, DMFS, DSS, OS	n.a.
Eckert et al. 2018 [32]	Prospective	42	50.4 Gy (45–50.4 Gy), adj. 60 Gy (50–66.4 Gy), def. 65 Gy (60–70 Gy)	2 × RHT/week or 2 × HT/week	Post-RHT	MR ther- mometry or intraluminal/ superficial/ interstitial thermometry	OS, DFS, DMFS, LC	n.a.
Unsoeld et al. 2020 [33]	Retrospective	48/11	50.0–50.4 Gy (1.8–2.0 Gy/fraction) Ifosfamide (d1 + d2)/ 4× Ifosfamide + doxorubicin	≈10HT/ patient, 90 min	5–6 weeks post-RT	MR-based thermometry	Pathologic response	n.a.
Spalek et al. 2021 [34]	Prospective, single-arm	30	Neoadj. 32.5 Gy (10 × 3.25 Gy) or 32.5 Gy (10 × 3.25 Gy)+ 16 Gy (4 × 4 Gy)	<1 h before RT, 2 × RHT or SHT/week for two weeks (+ 2× RHT or 2 × SHT/week for 1 week), 4 or 6 × HT in total	>6 weeks post- RT/RHT	Superficial and intraluminal thermometry for RHT, none for capacitive HT	RECIST criteria	CTCAE v.5.0
Rauch et al. 2021 [35]	Retrospective	136	Ifosfamide (d1–5), doxorubicin (d3) combined with 50 Gy + 10 Gy Boost + 1 × 2–2 × 1.5 Gy/day	2 × HT/week, 90 min	6 weeks post- HT	n.a.	RECIST and/or Choi (CR, PR, SD, PD)	n.a.
Willner et al. 2021 [36]	Retrospective	27	Ifosfamide (d1–5), doxorubicin (d3)combined with 45–75 Gy (1.5–1.8 Gy, ×5/week)	1–2 × HT/week, 1h	6-10 weeks post-CTX	MR-based thermometry	A-RFS, DMFS, DFS, OS	CTCAE v.4.0

CSS: Cause-Specific Survival; CTCAE: Common Terminology Criteria for Adverse Events; DLC: Duration of Local Control; DM: Distant Metastasis; DMFS: Distant Metastasis-Free Survival; LC: Local Control; MFS: Metastasis-Free Survival; OS: Overall Survival; pCR: Pathological Complete Response; RECIST: Response Evaluation Criteria in Solid Tumors; RFS: Relapse-Free Survival; RHT: Regional Hyperthermia; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group.

(1.8–2 Gy/fraction and boost radiations up to 66 Gy). Subsequently, patients received EIA or EIA + RHT in the context of post-induction therapy. The thermometry protocol is available in Issels et al. 1990 [37]and for all RHT treatments T_{90}, T_{50}, T_{20} and T_{max} were evaluated. The results indicated that patients that received RHT + EIA showed better local control rates (LPFS: HR= 0.58 and disease-free survival (DFS): HR = 0.70), and it is underlined that the positive impact of RHT is unrelated to the application of RT, which constitutes the most important local adjuvant treatment for high-risk STS. After a median follow-up of more than 11 years, in 2018, Issels et al. [20] showed that adding RHT to neoadjuvant EIA CTX improved LPFS compared to EIA CTX alone. Patients randomized to the CTX + RHT arm exhibited prolonged survival rates compared to those in the control arm of the study, who received CTX alone, with a 5-year OS of 62.7% vs 51.3% and a 10-year OS of 52.6% vs 42.7%, respectively ($p = 0.04$).

3.2. RHT combined with RT

In the trial by Leopold et al. 45 patients with stage IIA-IIIB according to the American Joint Comittee on Cancer Staging System for STS with 69% of them located in the lower extremity – were randomized in two therapeutic arms with one or two RHT/SHT sessions per week (5 and 10 RHT sessions respectively) combined with RT in neoadjuvant manner. SHT was applied on lesions located within 3 cm of the skin surface (Clinitherm system). In contrast, deeper lesions were treated with an annular microwave array (BSD system) or a non-focused ultrasound array (Labthermics system). Patients were stratified by tumor volume ($\leq$ 225 cm^3 and $>$225 cm^3). The patients received RHT/SHT, 30–60 min after RT (50–50.4 Gy in total in fractions of 1.8–2 Gy). The targeted treatment time of 60 min was started after the temperature of 42 °C was achieved 10 min after power onset and resulted in an average duration of 57–58 min. For the patients, who were included in the 2 × HT/week group, a 48-h interval between the sessions was applied. Throughout the trial, invasive, CT-guided thermometry was used, with a reported accuracy of 0.2°C. In addition to T_{min}, T_{max}, T_{10}, T_{50} and T_{90}, an extensive set of thermal dose parameters was calculated, including the cumulative minutes the temperature at which 50% and 90% of all measured temperatures were at or above target temperature (Cum min T_{50} or $T_{90} \geq temp_{index}$). Thereby, the authors were venturing to identify significant temperature/time effect correlations with the treatment outcome. From the 44 patients eligible for evaluation, 38% in the first group (1 × HT/week) and 79% in the group that received 2 × HT/week demonstrated striking ($\geq$ 80% tumor necrosis) histopathologic changes ($p = 0.007$). Still, these percentages were not translated into outcome-predictive variables.

Prosnitz et al. suggested that RHT in combination with neoadjuvant RT improved regional control for high-risk extremity and non-extremity STS. Specifically, 97 patients bearing grade 2 and 3 resectable STS were treated with neoadjuvant RT of 50 Gy in total (1.8–2 Gy/fraction) combined with 1xRHT or 2xRHT sessions per week, one hour after RT delivery. A radiofrequency annular phased array system delivered RHT (BSD 2000). Throughout the trial, the temperature was monitored through an intratumoral probe (CT-guided placement), and the CEM43° T_{90} parameter was assessed to evaluate the thermal dose, which in turn was correlated to the histological response (tumor necrosis percentage). The admissible range of the CEM43° T_{90} parameter was from 10 to 100 upon treatment planning. During the study, the protocol was adjusted so that all patients received 2 × RHT per week. Definitive resection was performed 4-6 weeks after RT + RHT. Eight patients received adjuvant, doxorubicin-based CTX. The efficacy of the therapeutic scheme was assessed radiographically or clinically, if applicable, on 74 out of the 97 patients with available follow-up data. The median follow-up period was 32 months (ranged from 12 to 155 months), and within 10 years, LC for extremity STS was 94% compared to the LC (63%) for the non-extremity STS.

In the trial of Maguire et al. 35 patients bearing high-grade STS, with Karnofsky Performance Status $\geq$ 70% received RT (total dose of 50–50.4 Gy, 1.8−2.0 Gy/fraction, 5x/week) combined with RHT (BSD 2000). This trial evaluated whether the delivery of a thermal dose of $\geq$10 CEM43° T_{90} combined with RT would trigger a pCR in $\geq$75% of the patients with high-grade STS. A trial RHT session of 1 h duration was applied to all the patients as a selection filter for non-heatable tumors. Specifically, according to the evaluation ofCEM43° T_{90}, patients were assorted either in the group which would not receive any RHT treatment (CEM43° $T_{90} < 0.5$ after 1 h of RHT) or in the group where 2xRHTweek were administered (CEM43° $T_{90} > 0.5$ after 1 h of RHT) for a maximum of 10 RHT sessions or until CEM43° $T_{90}>$ 100 was achieved. For the duration of the trial, the temperature was constantly monitored by interstitially placed probes. In conclusion, although the approach showed excellent local tumor control, the set percentage $\geq$ 75% was not achieved. Only 29 out of the 35 patients had evaluable responses, and only 52% had a pCR (> 80% tumor necrosis). This deviation from the target percentage could be due to the lack of reliable thermometry, the small samples of patients, or due to the unsuitable surrogate endpoint for tumor control.

Dewhirst et al. by exclusively applying neoadjuvant RHT + RT, explored parameters with predictive potential on patients' response. All 35 patients accrued for this trial had grade 2 and 3, untreated STS with diameter $\geq$5 cm (57% of the patients had STS $\geq$ 10 cm), and 29 out of the 35 patients' STS were in the extremities. The maximum number of RHT sessions was ten (2 × RHT/week), and a total dose of 30–50 Gy (1.8–2 Gy) of RT was administered within 5 weeks. All the patients had a Karnofsky Performance Status of $\geq$ 70%. Multipoint invasive thermometry was used for the measurement of temperature distribution. The treatment goal of the trial was to achieve a thermal dose of 10 CEM43° T_{90}. Patients were considered eligible for RHT treatment according to the same procedure as previously described by Maguire et al. During the trial, the predictive potential of magnetic resonance spectroscopy parameters (PME/PDE ratio) which features the metastatic potential of the cancer

cells, was examined. The rationale behind the use of PME/PDE as a metastasis predictor is that the resonance ratio would reflect the extent of cellular anabolism, and PME/PDE was shown to be lower in patients with metastatic tumors. The primary endpoint was the complete pathological response pCR, characterized by the percentage ($\geq$80%) of tumor necrosis. The HR for patients having PME/PDE $\geq$0.45 was 5.8 for metastasis-free survival (MFS) and 6.8 for OS, which is showing that the PME/PDE ratio has predictive potential[1]. Other magnetic resonance spectroscopy/magnetic resonance imaging (MRS/MRI) parameters and oxygenation data that were examined and correlated to the treatment outcomes were: intracellular pH, T2 relaxation time, and pO_2. The duration of RHT was not specified (the protocol [28] reports 1 to 2 h of RHT treatment).

In 2012, de Jong *et al*. reported the results on the feasibility of the re-RT of the RT-associated sarcomas (RAS) of the thorax in sixteen patients (twelve evaluable responses). De Jong showed an enhanced response rate of 75% in the twelve evaluable patients.

Specifically, seven patients exhibited complete and two partial responses, whereas six patients remained local-failure-free (LFF) until death. Complete response was defined as elimination of all lesions, while partial response referred to a 30% decrease in the sum of greatest dimensions of the target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients were treated in two cancer centers (Academic Medical Center - AMC and the Institute Verbeeten - BVI). The total RT dose at the AMC was 32 Gy (8×4 Gy) given twice per week for 4 weeks while at the BVI, patients received a total dose of 36 Gy (12×3 Gy) 4 times per week. RT was combined with SHT applied by microstrip applicators and the temperatures were measured superficially. The high response rate (75%) indicates that the combination of re-RT plus SHT in this approach leads to durable LC, and it can serve as a dynamic solution to a condition as rare as RAS sarcomas.

A retrospective study by Linthorst et al. published in 2013 showed that HT combined with re-RT of RAS could improve the local control rates with or without surgery. In 11 years, 24 patients diagnosed with RAS were treated with RT and SHT with or without surgery. Different equipment was used for the re-RT application within the patient population, depending on the centers they were assigned to, the grade/-stage of the tumors, the previous therapy status, and the clinical setting. The RT treatments were delivered before the SHT sessions using photons, electrons, or a combination of both. SHT treatments were delivered using contact flexible microstrip applicators (CFMA) and Lucite cone applicators. The treatment schemes consisted of neoadjuvant re-RT + SHT, surgery and adjuvant re- RT + SHT or re- RT + SHT alone (no surgery). The thermal parameters which were evaluated throughout the study using the interstitial temperature data were: the maximum (T_{max}) and the average temperature (T_{ave}), T_{90} and CEM43° T_{90}. Evaluating the data of the 24 patients, the group of patients that had undergone surgery (46%) before or after re-RT + SHT (neoadjuvant RT on 3/11 patients, adjuvant RT on 8/11 patients) presented a median survival time of 13 months compared to the 5 months of survival time for the re-RT + HT alone group of patients (13 inoperable patients). However, there was no statistical significance, possibly due to the small number of patients in the subgroup analysis.

In 2013, Eckert et al. retrospectively evaluated the outcomes of twenty-eight patients who were neoadjuvantly treated with RT of a median total dose of 45 Gy (44–56 Gy) alone or combined with simultaneous CTX and/or RHT. Half of the patient population had extremity sarcomas; the other half suffered truncal or head & neck sarcoma. Sixteen patients were treated with neoadjuvant RT alone, and the rest (twelve patients) followed a bimodal or trimodal approach. RT was performed as a 3-D conformal therapy, and in two cases, intensity-modulated radiotherapy was utilized. Ifosfamide was used for CRT or a combination of RHT and CRT. RHT was applied once or twice per week; no further specification is given. The endpoints assessed were LC, DFS, DMFS, and DSS. The data evaluation, 3 years after the completion of the treatment, showed no effect of bi- and trimodal treatment on LC or DFS. Nevertheless, DMFS and DSS seem to differ from the RT-alone group, with the DSS exhibiting statistically significant benefits for the multimodal group (100% vs 70%, $p = 0.03$). These results suggest that patients with high-risk STS can benefit when treated with RHT combined with neoadjuvant CRT. Information about thermometry and RT fractionation is not provided.

In 2018, Eckert et al. prospectively assessed the LC in patients with local recurrences who were treated within a multimodal setting. The analysis included forty-two patients, nine of who were treated for isolated local recurrences while the rest were treated for primary tumors. The CTX regimen consisted of ifosfamide alone or in combination with doxorubicin (to patients 65 years of age, bearing poorly differentiated STS). All patients eligible for HT were treated with RHT or SHT. RHT was applied twice per week using BSD 2000/3 D (Sigma-30/60/Eye or superficial SA115 applicator); the target temperatures were within the range of 40 °C−43 °C (60-90 min.) and the type of thermometry was dependent of the localization of the tumor, varying from superficial, intraluminal, or interstitially in the tumor. During the trial, age at the time of diagnosis/recurrence vs. initial diagnosis, localization, grading, resection status, additional sequential CTX, and concurrent radiosensitizing CTX were tested as prognostic factors along with their influence on the LC of the tumor. The median follow-up was 1.4 years. After 1.5 years, the exhibited DFS, DMFS and LC for the cohort were 66, 73, and 88%, respectively. The fraction of patients presenting significantly impaired LC was greater in the group treated multimodally for local recurrence after excision compared to the ones who were treated multimodally for primary tumors (100 vs. 52%, $p < 0.001$).

In 2020, Unsoeld et al. focused on MR thermometry and correlated its outcome to pathological responses of the tumor. They showed that larger, more responsive tumors reached higher temperatures compared to the rest due to better tolerability of RHT. This observation was proof of a dose-response relationship. Specifically, forty-eight patients

were treated in a neoadjuvant setting with RT + RHT in the context of this cohort, and in some cases, CTX was applied. All patients had grade II or III subfascial tumors and patients with retroperitoneal, abdominal and pelvic tumors were excluded, as they were not eligible for MR-based thermometry. Finally, 11 patients that had extremity sarcomas (calf and thigh) were included in the analysis of tumor volume (V_{Tu}) and a separate volume for temperature analysis with reliable MR thermometry readouts (V_{therm}). Out of these 11 patients, 6 received concomitant ifosfamide CTX according to the IAWS protocol. Evaluating the thermal parameters: $T_{90}(V_{Tu})$, $T_{50}(V_{Tu})$, $T_{10}(V_{Tu})$, CEM43(V_{Tu}), $T_{90}(V_{therm})$ and CEM43(V_{therm}), revealed that the mean of these parameters differed significantly in patients who had achieved a pathologic response. Reflecting on the above-given information, it is evident that MR-based thermometry is a convenient and more tolerable way to measure temperature during RHT sessions.

More recently (2021), Spalek et al. combined RHT (BSD-2000, $n = 7$) or capacitive HT (Celsius TCS, $n = 23$) with hypofractionated neoadjuvant RT of a total dose of 32.5 Gy (3.25 Gy/fraction) for locally advanced and marginally resectable STS. Patients bearing unresectable STS were also included in the trial. All thirty patients in the trial had an ECOG performance status from 0 to 2; they were bearing either chemoresistant or low-grade STS or were not eligible for CTX and did not present any contraindications to RT or RHT. After completing the therapy (RHT 2x/week + total 32.5 Gy 1 h post-RHT, >48 h break between two RHT sessions), patients who could not be referred to surgery underwent extra local treatment (total 16 Gy in 4 fractions + RHT 2x/week using BSD-2000, $n = 3$ & Celsius-TCS, $n = 11$). Local progression (LP), LPFS, sarcoma-specific survival (SSS) and PFS were 97%, 93%, 97% and 88%, respectively, after the 13 months follow-up. The results indicate that hypofractionated RT combined with RHT can effectively treat patients with chemoresistance or severe contradictions. The duration of the RHT treatments is not stated.

In a recent cohort study, Rauch et al. evaluated the benefits of neoadjuvant treatment in combination with excision for STS in 136 patients. Patients with unresectable or barely resectable high-risk STS were recruited in this trial. The neoadjuvant treatment was applied to 74 patients. It consisted of a total RT dose of 50 Gy and a 10 Gy booster (1×2 Gy or 2×1.5 Gy/day), and, for a subgroup of 66 patients (89%), it was combined with simultaneous CTX of ifosfamide and doxorubicin. Furthermore, 31 patients of this group (42%) received neoadjuvant RHT twice per week with a target temperature of 40-*44 °C* for 90 min. Primary surgery was applied to 62 patients, and 11 were adjuvantly treated with RHT. The latter constitutes the control arm of the cohort. Comparing the group of patients treated in a neoadjuvant manner to the 'primary surgery' group, the 5-year LRFS was slightly elevated in the first (90.5% vs 89.5%). At the same time, the 5-year MFS, DFS and OS rate was enhanced in the group that received primary surgery 67.2% vs 88.3%, 64.1% vs 78.4% and 62.8% vs 83.8%. Details about thermometry, the treatment sequence, or the equipment used are not reported.

Lastly, in the context of the Willner et al. study in 2021, 27 patients (ECOG >1 and/or age ≥80 years) who were bearing retroperitoneal sarcomas were treated with RHT + CTX±RT in a neoadjuvant manner. Specifically, all patients were treated with CTX (doxorubicin and ifosfamide) and RT (50.4 Gy, 1.5–1.8 Gy), and in 56% of the patients RHT was applied (BSD 2000) up to 44 °C for 60 min ×1–2/week, with or without noninvasive MR-thermometry; no further specification on the selection is given. After the 5- and 10-year follow-ups, the whole cohort exhibited high percentages of ARFS (74.6% – 66.3%) and DMFS (67.2% – 59.7%) which were not translated into OS benefit over the years (60.3%). RHT was administered for a median of five treatments parallel to the CRT arm. Patients that received less than 5 sessions presented elevated ARFS and DFS compared to the ones that received 5 sessions or more, who exhibited enhanced DMFS and OS. The differences were not significant. This led to the conclusion that integrating RHT in the therapeutic setting did not benefit the patients, indicating that neoadjuvant CRT, regardless of the implication of HT, could be feasible against high and intermediate-risk STS.

4. Discussion

In the present review, besides the randomized trial by Issels et al. [14], we identified 14 additional non-randomized reports, which integrated RHT + SHT into different therapeutic schemes and reported on pathological response and local control as primary endpoints.

4.1. Overview

Herein, we systematically review the current literature on RHT in the management of localized STS. The data, and particularly the phase III EORTC comparative study, clearly indicate a survival benefit for these patients (5-year OS of 62.7% vs 51.3% and a 10-year OS of 52.6% vs 42.7% in the presence of RHT, $p = 0.04$). In addition, some of the identified reports were retrospective case series, where the different level of available data made the analysis challenging.

We have identified data on the combined effects of RHT and RT showing a dose dependency (twice vs. one session per week increases striking histopathological changes from 38% to 79%, $p = 0.007$) for the RT enhancing effect of RHT. Contemporary data showed the feasibility of incorporating neoadjuvant RCT and RHT, indicating that both, enhancement of neoadjuvant CTX and RT, is possible by RHT [32]. Whether neoadjuvant RCT + RHT is more effective compared to neoadjuvant CTX + RHT, is currently not known.

In the present review, there are cases where the choice of chemotherapeutic drugs is not standard of care any more, details about the combination are missing or, in cases of elective administration, the criteria are not clearly stated. In most of the trials where CTX was incorporated, doxorubicin-based schemes were preferred. Furthermore, in cases where off-the-protocol CTX was administered, the patient selection criteria for that and the structure of the CTX scheme are not stated [25]. In the EORTC 62961-ESHO 95 – RHT95, RHT was

Table 4. Haussmann compared the therapeutic regimes used in 25 STS clinical trials.

Haussmann comparison of different STS therapies				
Experimental arm	OS (HR)	DFS (HR)	LRFSI (OR)	DRFS (OR)
Surgery ± RT + Adjuvant CTX	0.86 ($p = 0.017$)	0.76 ($p < 0.001$)	0.76 ($p = 0.03$)	0.71 ($p = 0.001$)
NACTX + RHT + Surgery ± RT	0.45 ($p = 0.049$)	0.52 ($p = 0.046$)	0.51 ($p = 0.183$)	0.67 ($p = 0.349$)
NACTX + Surgery ± RT	0.61 ($p = 0.195$)	0.73 ($p = 0.298$)	0.82 ($p = 0.653$)	0.74 ($p = 0.388$)
Tailored NACTX + Surgery ± RT	1.08 ($p = 0.868$)	0.9 ($p = 0.765$)	1.34 ($p = 0.646$)	1.52 ($p = 0.385$)
CTX + Surgery ± RT + CTXX	0.66 ($p = 0.317$)	0.72 ($p = 0.322$)	0.55 ($p = 0.342$)	0.78 ($p = 0.548$)

CTX: Chemotherapy; DFS: Disease-Free Survival; DRFS: Distance Relapse-Free Survival; HR: Hazards Ratio; LRFSI: Local Relapse-Free Survival Interval; NACTX: Neo-Adjuvant Chemotherapy; OR: Odds Ratio; OS: Overall Survival; RT: Radiotherapy.

combined with four cycles of neoadjuvant and adjuvant CTX, however today usually six cycles of neoadjuvant CTX are regarded as standard of care. In addition, RHT was combined with three CTX drugs but today only doxorubicin and ifosfamide are usually used. Thirdly, adjuvant RT was applied but not combined with RHT aiming to gain further synergistic effect.

STS therapeutic strategies are tailored around excision which remains the main and most critical step of handling STS. Nevertheless, there are cases where the sequence of the treatment is not explicit [35] or, regarding adjuvant therapies, the time interval between the excision and the subsequent treatment modalities are not stated [25]. Additionally, systematically reported information about thermometry would help improve the overall quality of RHT treatment. However, in studies where invasive thermometry is used, which stands as a controversial topic, only a few information exists about direct effects like local infection or cancer dissemination incidences over time. In the case of the promising MR-based thermometry, there are still some complications and difficulties since not all RHT applicators are compatible with the method and more importantly, technically MR-based thermometry is currently only feasible for macroscopic tumors of the lower extremities [33]. Lastly, open questions regarding the incidence of thermotolerance in case of high number of RHT sessions per week still remain.

Ultimately, apart from the questions that rose from the literature of the present review, there are more aspects that need to be clarified. An example would be the definitions for RHT contraindications. For instance, regarding metal implants, the maximal length and minimal distance to the applicator remain to be defined. Regarding cardiovascular comorbidity, it varies from study to study regarding the magnitude of cardiac insufficiency considered as a contraindication.

4.2. Further evidence

Apart from the information in this review, there is further evidence of the beneficial role of RHT on the treatment of STS. In 2021, Haussmann et al. [38] published the results of a major network meta-analysis of 25 trials, comparing different systemic treatments in STS. The Haussmann analysis compared the basic treatment (surgery ± RT) and the different experimental arms as shown in Table 4. According to these results, adding RHT led to significantly favorable results for the patients in the experimental arm, with enhanced DFS, LRFS, DRS, and OS, when directly compared to neoadjuvant CTX + Surgery ± RT and indirectly to surgery ± RT.

Published in 2021, Issels et al. [39] conducted a translational subanalysis of the EORTC 62961-ESHO 95 – RHT95 randomized clinical trial. The authors analyzed tumor samples from patients in both treatment groups to determine the presence and distribution of immune cells within the tumor microenvironment. They found that patients who received neoadjuvant CTX and RHT had a significantly higher density of CD8+ cells within the tumor than those who received CTX alone. Also, RHT induced the expression of genes associated with immune cell activation and recruitment, suggesting that RHT may enhance the anti-tumor immune response. These findings are providing a deeper insight on RHT mode of action and suggest that it may play an essential role in stimulating the immune response to STS. Based on the above, RHT could be used as a therapeutic strategy to improve outcomes in patients with high-risk STS.

4.3. Upcoming data

Currently, there are nine active clinical studies which are focusing on the impact of HT on STS. Nevertheless, only two of them have incorporated RHT in their therapeutic regime. The HyperTET (NCT02359474) trial is a Phase II, interventional trial which is organized and performed in Ludwig-Maximilians - University of Munich. HyperTET started at the end of 2014 and it is expected to be completed in 2023. This study is evaluating patients with high-risk soft tissue sarcoma receiving trabectedin alone versus trabectedin in combination with RHT. PFS is the primary endpoint of this study while: Radiological response according to RECIST criteria, OS and treatment related toxicity (hematological, renal, hepatic, etc.), constitute the secondary outcome measures.

The second study is an interventional, Phase I trial which started in 2023 and it is expected to be completed by 2024. The trial (NCT05858710) is testing a thermosensitive liposomal formulation of the well-established chemotherapeutic drug doxorubicin (DPPG2-TSL-DOX), as a novel drug candidate. Unlike conventional liposomes, it has a different mechanism of action and this technology allows for intravascular drug release induced by mild heat through the use of clinically proven hyperthermia machines. The aim of this study is to improve clinical treatment efficacy by creating a local boost at the desired site of action, resulting in up to 15 times higher local drug concentrations in the site of STS. The primary outcome of the trial is the assessment of the maximum tolerated dose of the novel drug and the secondary outcome measures focus on the treatment-emergent adverse events and toxicities (according to CTCAE 5.0).

5. Conclusions

The present review shows that STS are one of the major indications for RHT integration to current therapeutic regimens. Nevertheless, there are still important open questions for instance regarding the combination of RCT and RHT and its combined effectiveness, the definition of contraindications for RHT and thermometry requirements. To further analyze these discrepancies a questionnaire and direct contacting of high-volume European STS centers with access to RHT is indicated and will lead to establishing and implementing a uniform and concordant therapeutic protocol in the clinical setting.

Note

1. HR: estimate of the risk of dying. HR = 5.8 for MFS shows: if PME/PDE > 0.45, then the relative risk of dying would be 5.8-fold greater than if PME/PDE < 0.45. Similarly for OS, HR = 6.8 for OS shows: if PME/PDE > 0.45, then the relative risk of dying would be 6.8-fold greater than if PME/PDE < 0.45.

Authors' contributions

Conceptualization and Supervision: Prof. Ghadjar P.
Investigation, data acquisition and analysis: All authors
Writing – original draft preparation: Veltsista D. P.
Writing – review and editing: All authors.
All authors have read and agreed to the published version of the manuscript.

Ethical approval

Due to the nature of this paper and its methodology, no institutional review board approval was required.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This project was supported by the H2020 Marie Sklodowska–Curie program—HYPERBOOST (project number 955625). The trial is financialy supported by Thermosome GmbH.

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