EUnetHTA Joint Action 3 WP4

**Rapid assessment of other technologies using the HTA Core Model®
for Rapid Relative Effectiveness Assessment**

REGIONAL HYPERTHERMIA FOR HIGH-RISK SOFT TISSUE SARCOMA TREATMENT

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and in no way represents the official opinion of the participating institutions or individuals.

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External clinical experts (Dr. S. Bodis, Dr. F. Lohr, Dr. J.P. Poulsen) provided input to the development of the Project Plan, provided advice to the assessment team during the assessment and

provided feedback on the draft assessment report. One additional clinical expert (Dr. T. Hølmebakk) was invited to provide feedback on the draft assessment report during the process. The project manager invited national and European patient organisations to participate in the assessment but did not receive any indication of interest from patients or patient organisations. We also invited producers of CE-approved medical devices that are used for regional hyperthermia. The table below lists the manufacturers that provided feedback on the draft project plan and/or the draft assessment.

Gyri Hval Straumann, information specialist from NIPHNO, developed the search strategy and conducted the search. Esther Elena García Carpintero, information specialist from AETS-ISCIII, critically appraised the search strategy and reviewed the information retrieval process. Christopher James Rose, statistician from NIPHNO, provided advice when planning the statistical analysis and when analysing the data from the selected studies.

Haukeland University Hospital in Bergen, Norway requested the health technology assessment on this topic through the National System for the Introduction of New Health Technologies within the Specialist Health Service in Norway. This organisation provided feedback on the project plan to ensure that this assessment covered its information needs. We also invited this organisation to provide feedback on the draft assessment.

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Conflicts of interest

All authors, co-authors, dedicated reviewers and external experts participating in this project have signed the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

Authors, co-authors and dedicated reviewers have declared that they have no conflicts of interest in relation to the technology and comparator assessed.

Among the four external experts, two persons had no relevant conflicts of interest to disclose (Dr. Jan Peter Poulsen, Dr. Toto Hølmebakk) and two experts have conflicts of interest to disclose. Dr.

S. Bodis is involved in an ongoing study (not industry sponsored) that is potentially relevant to the Effectiveness (EFF) domain. The study is ongoing and data were not available for inclusion in this assessment. Dr. F. Lohr has been employed by the company C-Rad (member of the board of directors), which produces devices for radiotherapy. In our assessment, radiotherapy is part of both the intervention (in combination with hyperthermia) and comparator group. We are not conducting a head-to-head comparison of hyperthermia versus radiotherapy. Experts with conflicts of interest are allowed to provide input for all aspects of the assessment, although decision-making throughout the production process is reserved to the assessment team (authors, co-authors and dedicated reviewers) that have no conflicts of interest.

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LIST OF ACRONYMS

AE	Adverse Event(s)
AETS-ISCIII	Instituto de Salud Carlos III
ASCO	American Society of Clinical Oncology
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CUR	Health problem and current use of technology
EFF	Clinical Effectiveness
EMEA	Europe, the Middle East and Africa
ESHO	European Society for Hyperthermic Oncology
ESMO	European Society for Medical Oncology
FNCLCC	French Fédération Nationale des Centres de Lutte Contre le Cancer
GIST	Gastrointestinal stromal tumour
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HHV8	Human gamma herpes virus 8
HR	Hazard Ratio
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ISM	Industrial Scientific and Medical
ITT	Intention to Treat
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
MeSH	Medical Subject Headings
MPNST	Malignant peripheral nerve sheath tumour
NCI	United States National Cancer Institute
NIPHNO	Norwegian Institute of Public Health
PICO	Patient, Intervention, Comparison, Outcome
POP	Planned and ongoing project database
RCT	Randomised Controlled Trial
RD	Risk Difference
REA	Relative Effectiveness Assessment
RER	Regione Emilia-Romagna
RF	Radio frequency
ROBINS-I tool	Risk of bias in non-randomized studies – of interventions
RR	Relative Risk
RT	Radiation Therapy
SAF	Safety

SNHTA	Swiss Network for Health Technology Assessment
STS	Soft Tissue Sarcoma
TEC	Description and technical characteristics of the technology
VASPVT	State Health Care Accreditation Agency

SUMMARY OF RELATIVE EFFECTIVENESS OF REGIONAL HYPERTHERMIA FOR HIGH-RISK SOFT TISSUE SARCOMA TREATMENT

Scope

This assessment addressed the following research question: Is the regional application of non-invasive external hyperthermia administered in addition to chemo- and/or radiotherapy more effective and/or safer for oncological patients with high-risk soft tissue sarcoma than radio- and/or chemotherapy alone. A detailed description of the scope can be found here: Scope.

Introduction

Description of technology and comparators

The technology under assessment is regional hyperthermia added to conventional therapies to treat high-risk soft tissue sarcoma (STS). Conventional therapies, considered as a comparator when used without hyperthermia, include adjuvant or neoadjuvant chemotherapy and/or radiotherapy.

Surgery remains the mainstay of treatment and is a prerequisite for curing most types of STS, supported by advanced multimodal therapies aimed at reducing the risk of local and distant recurrence.[1, 2] Chemotherapy, radiation therapy, or both, may be given before surgery.[3, 4] This neoadjuvant treatment approach can be used to shrink a tumour so that it can be removed completely, or to treat high-grade STS when there is a high risk of the cancer spreading. Chemotherapy and/or radiation may also be used after surgery. In such cases, the goal of adjuvant treatment is to kill any cancer cells that may remain in the body in order to lower the risk of the cancer returning.

Radiation therapy can be the main treatment for sarcoma in a patient who is not healthy enough to have surgery. External beam radiation is the most commonly used treatment for STS.[5] Chemotherapy for STS generally uses a combination of several anti-cancer drugs. Doxorubicin (Adriamycin) is the most commonly used drug, alone as standard first-line chemotherapy or in combination with ifosfamide (Ifex), which can also be used as a single agent in selected cases.[6] Targeted therapies are also used when specific types of STS appear to be more sensitive to certain drugs.[7]

Hyperthermia treatment aims to increase the temperature in target tissue to levels above normal systemic temperature, [8, 9] making it more likely to be affected by other treatments, such as chemotherapy or radiation therapy.[10, 11] Hyperthermia treatments can be local, regional (superficial and deep) or whole body depending on the extent of the area being treated. In regional HT a part of the body, such as an organ, limb or body cavity is heated. Regional HT for STS is always applied in addition to radiotherapy or chemotherapy, or both, but is not effective as a single treatment.[12-14] Available technologies that provide regional hyperthermia include radio waves, microwaves, ultrasound waves and other forms of energy used to heat the tumour area, although radiofrequency hyperthermia devices are the most used.[15, 16] Radiofrequency hyperthermia devices can be classified into radiative and capacitive technologies.[9, 16] [B0001]

Using information in the documentation of companies that manufacture HT systems for oncology as a reference, the claimed benefits associated with these treatments can be summarised as: i) improvement and extension of medical tumour control, ii) significantly higher success rates for treatment with chemotherapy and radiotherapy, iii) reduction of the tumour size enabling removal by surgery, iv) destruction of tumour cells, especially in cases of previously treatment-resistant tumours, v) increased remission rates and improved quality of life, vi) long-term improvement of the course of the illness and vii) reduced risk of metastases.[B0002]

Health problem

This assessment is focused on high-risk localised resectable STS eligible for neoadjuvant and/or adjuvant chemo-radiotherapy, localised unresectable and inoperable advanced metastatic STS treated with chemotherapy/radiotherapy only, diagnosed in adults.[A0002][A0007]

Adult STSs (excluding gastrointestinal stromal tumour (GIST)) are rare tumours, accounting for less than 1% of all new incident cancer cases, with an estimated incidence averaging 4–5/100,000/year in Europe,[17] and a median incidence age of 59 years.[18] [A0023]

High-risk STS is a subgroup of sarcomas that originate from soft tissue and harbour an increased risk of local recurrence and distant metastases following treatment, resulting in high tumour-related mortality. There is no universally accepted definition of high-risk STS. According to the European Society for Medical Oncology (ESMO), high-risk sarcomas are defined as high-grade malignant tumours, situated deep to the subcutaneous fascia and large (size > 5cm).[3] Within this assessment we included high-risk STSs occurring in different locations, i.e. extremity, trunk, head and neck, and retroperitoneal, excluding GIST.[19, 20] [A0002]

STS clinically presents as a gradually enlarging, painless mass that can become quite large before causing symptoms. The most common symptoms are pain, paraesthesia or oedema in an extremity, generally associated with compression by the mass. Constitutional symptoms, such as fever and weight loss, are rare at diagnosis.[A0005]

Because of their rarity and the frequent need for multimodality treatment, guidelines recommend that evaluation and management of STS should ideally be carried out at a centre with expertise in the treatment of sarcomas, including surgical oncology, orthopaedic surgery, plastic surgery, adult or paediatric medical oncology, radiation oncology, and a high volume of treated patients. Imaging of the affected site should include MRI, plain radiographs, CT and/or PET.[21] Following imaging assessment, the standard approach to diagnosing STS is to perform biopsies and a pathological examination that should be carried out by a specialist sarcoma pathologist.[A0024]

The major therapeutic goals in patients with STS are survival, avoidance of local recurrence, maximizing function and minimizing morbidity.[22, 23]

Methods

After an initial search for existing evidence syntheses, we systematically searched for primary studies in the following databases: Medline (Ovid), Embase (Ovid), Cochrane Central Register of Controlled Trials, AMED. We also searched for terminated, unpublished and ongoing primary studies at clinicaltrials.gov and WHO ICTRP. The detailed search strategy is available in Appendix 1. In addition to the systematic search, we also considered information derived from clinical practice guidelines, information from a general literature search and input from clinical experts and manufacturers to complete the TEC and CUR domains.

Two reviewers independently screened studies retrieved through the literature search against the predefined criteria. One reviewer used a pre-established form to extract data from the selected studies, with a detailed revision by another reviewer. For randomized controlled trials (RCT), two reviewers independently appraised the risk of bias on study and outcome level using the Cochrane Risk of Bias tool.[24] For non-randomised studies we used the ROBINS-I tool (Risk of Bias in non-randomized studies – of interventions).[25] To rate the certainty of the evidence for each outcome, we used GRADE (Grading of Recommendations, Assessment, Development and Evaluation).[26] For the TEC and CUR domains, no quality tool was used. Clinical experts and manufacturers reviewed the descriptions provided in this report. We aimed to involve patients, but had no positive response to our invitations to participate.

According to the GRADE approach, we graded the importance of each outcome through a structured process. To interpret the magnitude of effect sizes we have screened the literature to identify accepted standards for minimal important differences for the outcomes that we selected in this assessment. Within this context we identified the clinically meaningful outcomes for cancer trials defined by the American Society of Clinical Oncology (ASCO).[27]

Results

Available evidence

For the effectiveness domain we used evidence from the EORTC RCT (NCT 00003052).[28, 29] The EORTC RCT enrolled 341 patients from nine centres in four countries (six centres in Germany, one in Norway, one in Austria, one in the USA). The patients were randomised equally to an intervention group that received four cycles of chemotherapy + regional hyperthermia neoadjuvantly, followed by the best local therapy (surgery and/or radiotherapy) and adjuvant chemotherapy + regional hyperthermia, or to the comparison group that received the same procedures without regional hyperthermia. Median follow-up times for the outcomes reported in EORTC 2010 were three years in the intervention group receiving hyperthermia and 2.6 years in the control group. The median follow-up duration in EORTC 2018 was 11.3 years (interquartile range 9.2–14.7 years).

For the safety domain we had evidence from the EORTC RCT and from ten single-arm studies. The single-arm studies were published between 1995 and 2015 and included a median of 20 patients (range 6–97). Follow-up times ranged from 8 months to 17.6 years.

Given that only one RCT (containing two publications) and ten single-arm trials were found, we conducted no meta-analysis. Instead, we provided a descriptive analysis of the data.

Clinical effectiveness

EORTC 2010 reported 44% deaths in the intervention group, 46% in the comparison group and a hazard ratio (HR) for overall survival of 0.88 (95% Confidence Interval (CI) 0.64, 1.21). The median survival duration was reported to be 6.6 years (95% CI 4.5, >10) in the intervention group versus 6.1 years (95% CI 3.8, >10) in the comparison group. EORTC 2018 reported 54% deaths in the intervention group versus 61% in the comparison group. No HR or time-to-event data were provided for overall survival.[D0001]

EORTC 2018 reported disease-specific survival with a median duration of 15.4 years (95% CI 6.6, >17.0) in the intervention group and 6.2 years (95% CI 3.2, 10.3) in the comparison group with an HR of 0.73 (95% CI,0.54, 0.98). The proportion of patients with death from disease or treatment was 48% in the intervention group versus 58% in the comparison group. Survival rate in the intervention group at 10 years was 53% versus 43% in the comparison group (Risk difference (RD) 10% (95% CI -1, 21%).[D0001]

EORTC 2010 reported an objective response rate of 29% in the intervention group and 13% in the comparison group (RD 16%, 95% CI 6, 26%). EORTC 2018 reported 30% in the intervention group and 13% in the comparison group (RD 17%, 95% CI 7, 27%).[D0005]

EORTC 2018 reported an HR for disease-free survival of 0.71 (95% CI 0.55, 0.93). The median duration of disease-free survival was 2.8 years in the intervention group (95% CI 2.0, 4.9) and 1.5 years in the comparison group (95% CI 1.1, 2.1). The proportion of patients with disease-free survival at two years was 58% in the intervention group and 44% in the comparison group (RD 14%, 95% CI 3, 24%). At four years, these proportions were 42% and 35%, respectively (RD 7%, 95% CI -3, 17%).[D0006]

EORTC 2018 reported an HR for progression-free survival of 0.65 (95% CI 0.49, 0.86). The median duration of progression-free survival was 5.6 years (95% CI 2.9, 8.7) in the intervention group and 2.4 years (95% CI 1.7, 4.2) in the comparison group. The proportion of patients with progression-free survival at two years was 76% in the intervention group and 61% in the comparison group (RD 15%, 95% CI 6, 25%). At four years, these proportions were 66% and 55% (RD 11%, 95% CI 1, 21%).[D0006]

EORTC 2018 reported that within the intervention group, 9% needed an amputation versus 11% in the comparison group (RD -2%, 95% CI -11, 7%).[D0011]

Safety

EORTC 2018 reported on 3.1% of patients who died due to adverse events in the hyperthermia group and 1.2% in the comparison group (RD 2%, 95% CI -1, 5%).[28] Median follow-up was 11 years. Two single-arm trials included data on deaths related to adverse events.[30, 31] In Prosnitz 1999, 3.1% (95% CI 1, 9%) of patients died due to complications within a median follow-up period of 2.6 years (range 1–12.9 years). In Hayashi 2015, all patients were alive (95% CI 0, 46%) after a mean follow-up period of 10.9 years (range 8.1–17.6 years).[C0008]

EORTC 2010 reported grade 3–4 haematological toxicities, nephrotoxicities, cardiotoxicities, neurotoxicities, gastrointestinal toxicities, infections, musculoskeletal and connective tissue disorders, injuries and general disorders.[29] Frequencies for each type of toxicity and other adverse events are available in Table 6-2.[C0008]

Ethical, organisational, patient and social and legal aspects

The use of devices for regional hyperthermia requires the establishment of specialised centres of administration. This could create organisational issues and ethical issues because of reduced access for geographical reasons. A STS diagnosis has important financial and social impact for patients. Introduction of hyperthermia technology could increase these impacts. From a legal perspective, treatment with hyperthermia devices may require the use of a documented informed consent process.

Upcoming evidence

We identified three ongoing studies, including one RCT (HyperTET NCT02359474) that compares hyperthermia and chemotherapy to chemotherapy only and two single-arm trials (HYPROSAR NCT01904565, UMIN000013056). It is not clear when these studies will be completed. This assessment team is committed to updating the report once the results of these studies are available.

Reimbursement

Within Europe, the technology can be reimbursed in specific clinical situations in Germany, Switzerland, the Netherlands, Italy, Poland and Czech Republic. As for other EU countries, we have limited or no information: the technology is either not reimbursed or decisions may be at local level. In the USA, hyperthermia is reimbursed as a palliative treatment of various solid tumours (superficial hyperthermia) and for the treatment of advanced cervical cancer patients who cannot tolerate chemotherapy (deep hyperthermia).[A0021]

Table 0-1: Summary of findings – table of regional hyperthermia

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with hyperthermia	Difference				
Effectiveness							
Overall survival							
EORTC trial (median follow-up 3y)				HR 0.88 (0.64, 1.21)	341 (1 study)	Low [1,2,3]	Intermediate data, median not reached ASCO minimal important differences for cancer trials define a HR for overall survival of 0.8 or less, minimum 25% increase in median overall survival
	Median survival 6.1y (3.8, >10)	6.6y (4.5, >10)	0.5y more				
	Survival 2y 72%	78%	6% more (-3 to 15)	RR 1.08 (0.96, 1.22)			
	Survival 4y 57%	59%	2% more (-8 to 13)	RR 1.04 (0.87, 1.24)			
EORTC trial (median follow-up 11y)	Deaths 61%	54%	7% less (-17 to 4)	RR 0.89 (0.74, 1.07)	329 (1 study)	Low [1,2]	
Disease-specific survival							
EORTC trial (median follow-up 11y)				HR 0.73 (0.54, 0.98)	329 (1 study)	Low [1,2,3]	
	Median survival 6.2y (3.2, 10.3)	15.4y (6.6, >17.0)	9.2y more				
	Survival 5y 51.3%	62.7%	11% more (1 to 22)	RR 1.22 (1.01, 1.48)			
	Survival 10y 42.7%	52.6%	10% more (-1 to 21)	RR 1.23 (0.98, 1.55)			

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with hyperthermia	Difference				
Disease-free survival [4]							
EORTC trial (median follow-up 3y)	DFS 2y 44%	58%	14% more (3 to 24)	RR 1.31 (1.06, 1.62)	341 (1 study)	Low [1,2,3]	
	DFS 4y 35%	42%	7% more (-3 to 17)	RR 1.20 (0.92, 1.58)			
EORTC trial (median follow-up 11y)				HR 0.71 (95% CI 0.55, 0.93)	329 (1 study)	Low [1,2,3]	
	Median DFS 1.5y (1.1, 2.1)	2.8y (2.0, 4.9)	1.3y more				
Progression-free survival [4]							
EORTC trial (median follow-up 3y)	PFS 2y 61%	76%	15% more (6 to 25)	RR 1.25 (1.08, 1.45)	341 (1 study)	Low [1,2,3]	
	PFS 4y 55%	66%	11% more (1 to 21)	RR 1.20 (1.01, 1.43)			
EORTC trial (median follow-up 11y)				HR 0.65 (0.49, 0.86)	329 (1 study)	Low [1,2,3]	
	Median PFS 2.4y (1.7, 4.2)	5.6y (2.9, 8.7)	3.2y more				
Amputation [5]							
EORTC trial (median follow-up 3y)	9%	7%	2% less (-10 to 5)	RR 0.76 (0.29, 1.95)	206 (1 study)	Low [1,2,3]	
EORTC trial (median follow-up 11y)	11%	9%	2% less (-11 to 7)	RR 0.84 (0.33, 2.14)	166 (1 study)	Low [1,2,3]	
Health-related quality of life							Outcome not assessed

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with hyperthermia	Difference				
Pain							Outcome not assessed
Objective response rate							
EORTC 2010 (median follow-up 3y)	13%	29%	16% more (6 to 26)	RR 2.27 (1.31, 3.89)	244 (1 study)	Low [1,2]	
EORTC trial (median follow-up 11y)	13%	30%	17% more (7 to 27)	RR 2.31 (1.35, 3.95)	238 (1 study)	Low [1,2]	
Fatigue							Outcome not assessed
Motor function							Outcome not assessed
Neurological function							Outcome not assessed
Psychological well-being of patients							Outcome not assessed
Rate of local tumour control							Outcome not assessed
Local tumour recurrence							Outcome not assessed
Safety							
Death related to AE							
EORTC trial (median follow-up 11.3y)	1.2%	3.1%	2% more deaths by AE (-1 to 5 more)	RR 2.58 (0.51, 13.09)	329 (1 study)	Low [1,3]	
Single-arm studies (Follow-up range 1–17.6y)		0% (0 to 46) 3% (1 to 9)			103 (2 studies)	Very low [1,3,7]	

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with hyperthermia	Difference				
Severe to life-threatening AE (grade 3 to 4)							
EORTC trial (median follow-up 3y)	Severe to life-threatening AE in the following categories: haematological toxicities, nephrotoxicities, cardiotoxicities, neurotoxicities, gastrointestinal toxicities, infections, musculoskeletal and connective tissue disorders, injuries and general disorders as described in Table 6-2.				329 (1 study)	Very low [1,3,8]	
Single-arm studies		Severe to life-threatening AEs present in every study AE/patient 0.23–1.8 (2 studies) Range patients with AE 14–100% (2 studies) Amputation due to AE RD 4% (1 to 10) and RD 7% (0.2 to 34) (2 studies)			312 (10 studies)	Very low [1,3,7,9]	
Other outcomes							
Patient satisfaction							Outcome not assessed
Shared decision-making measures							Outcome not assessed
Resource use							Outcome not assessed

1 Downgraded because of limitations in study design.
2 Unable to evaluate inconsistency because there is only one RCT. GRADE suggests particularly careful scrutiny of all relevant issues when only a single RCT addresses a particular question.[32]
3 The 95% confidence interval presents a large imprecision.
4 The survival benefit has been analysed as overall survival at the 3y follow-up and as death from disease or its treatment at the 11y follow-up.
5 Denominator is patients that received definitive surgical resection.

6 Denominator is patients with measurable disease.
7 Downgraded because of risk of publication bias (completed but unpublished study and 10 potentially relevant conference abstracts without full text) and downgraded because of partial reporting of adverse events which do not cover all the treatment components.
8 Downgraded because of partial reporting of adverse events which do not cover all the treatment components.
9 Downgraded because of heterogeneity in frequencies for the reported adverse events.

Abbreviations: CI Confidence Interval; DFS Disease-free survival; PFS Progression-free survival; HR Hazard ratio; RR Relative Risk; AE Adverse event

Discussion

We selected overall survival as the main endpoint of this assessment. In terms of overall survival, hyperthermia combined with chemotherapy and radiotherapy may not provide an important benefit versus chemotherapy and radiotherapy only. In the EORTC 2010 report, the point estimate for the hazard ratio and for the median survival time did not reach the ASCO thresholds for clinical significance. It is important to note that these data for overall survival are intermediate data. More than one half of the patients were still alive in the comparison groups, implying that the authors were not yet aware of the median value and that the follow-up period in EORTC 2010 was too short to observe any effects from hyperthermia.

In EORTC 2018, the trial authors switched from reporting overall survival to disease-specific survival. In the paper, the authors state that their motivation to switch was because the 20-year data set included a large number of older patients at increased risk of death from other causes. This increased risk of death from other causes in aging trial populations is a complication in clinical research that has led to developments in competing risk methodology. Competing risks in medical research occur when the time to a disease-specific endpoint of interest may be precluded by death or a major health event from another cause.[33] The EORTC 2018 reported outcomes that were better when the treatment was combined with hyperthermia, but did not adjust for competing risks. This could have led to flawed effect estimates. In general, when survival outcomes do not account for competing risks, the results tend to be overestimated.[34] Around 4% of patients died from other causes in EORTC 2018. There are currently no guidelines regarding what magnitude of competing events is problematic and likely to result in biased estimates when analysed using conventional statistical methods.[34] This failure to address competing risks may also have affected the results for progression-free survival and disease-free survival from EORTC 2018, which were favourable for the treatment combined with hyperthermia.

Deaths from adverse events were higher in the hyperthermia group with two more deaths per 100 patients (95% CI -1, 5%). In EORTC 2010, the authors hypothesized that this might be due to bone marrow suppression. The EORTC trial reported severe to life-threatening adverse events in multiple clinical categories. Hyperthermia increased the risk of leukopenia. For the other toxicities, the 95% CI was wide, including values that pointed at both increased or reduced harm. Severe to life-threatening adverse events were reported in all the single-arm studies.

We rated the certainty of the evidence for each of the outcomes of the effectiveness domain as low. For deaths from adverse events we rated the certainty as low and as very low for each of the other adverse event outcomes.

The identified studies only partially match the predefined scope of this assessment. Multiple predefined outcomes that the assessment team rated as critical or important for decision-making were not measured by the currently available evidence.

Conclusion

The claimed benefits of hyperthermia for high-risk STS cannot be confirmed or rejected by the currently available evidence.

Only one RCT assessed the effectiveness of this technology. It found improvements in disease-free survival, progression-free survival and disease-specific survival, but the analysis did not adjust for competing risk and the effect estimates may be flawed. No important effects were found

for overall short-term survival, although the effect estimates were very imprecise, including both clinically meaningful benefit and harm. These estimates were based on intermediate data. No long-term data on overall survival have been published. Further research is very likely to have an important impact, which is likely to change the estimate of the effect.

Hyperthermia combined with chemotherapy and/or radiotherapy may lead to increased harm, including death from adverse events and severe leukopenia. The estimates are very uncertain.

1 SCOPE

1.1 Description

Description	Project Scope
Population	Adults (>18 years) who have a high-risk STS. We excluded adolescents or children since treatment in these age groups follows specific paediatric protocols. STS represents a type of cancer that can occur in soft tissues (for example, muscles, nerves, blood vessels, fat tissues, etc.) in any part of the body. There are approximately 100 different types of STS based on the location and based on the type of soft tissue involved. Within this assessment we included the various types of STS in different locations, i.e. extremity, trunk, head and neck, and retroperitoneal. We excluded GIST because they are a sarcoma entity with unique biological features and with different treatment approaches. Surgical excision of tumour tissue is the most important part of the overall treatment of patients with STS, but achieving a clear surgical resection is not always possible. In this assessment, we included both patients with non-resectable tumours and with tumours that can be surgically resected. High-risk STSs harbour an increased risk of local recurrence and distant metastases following surgical resection, resulting in high tumour-related mortality. We used the criteria from the European Society for Medical Oncology (ESMO) guidelines, defining high-risk sarcoma as tumours which are high-grade malignant, situated deep (either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia) to the subcutaneous fascia and large (size > 5 cm).[35] This excluded studies that focus on low risk sarcoma, which do not require radiotherapy or chemotherapy, meaning small, superficial, low-grade tumours. The two most widely used systems for grading sarcoma are the NCI (United States National Cancer Institute) system and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system.[36, 37] We also identified the Sarculator as a tool for predicting the probability of overall survival and incidence of distant metastasis for patients with STS.[38] Given that there is no universally accepted definition of high-risk sarcoma, we also included high-risk classifications using the Sarculator, which is based on patient age and tumour histology, size and grade. Within this assessment we included both localized and metastatic sarcomas in which the cancer has spread from the main tumours to other areas. We included patients undergoing curative treatment and patients undergoing palliative treatment. In the case of studies with a mixed population (i.e. low and high risk), we did not include studies if less than 75% of the included patients were considered to be high-risk STS patients, unless they provided stratified results that enabled the extrapolation of data on high-risk patients. Intended use of the technology: Specialist healthcare International Classification of Diseases (ICD) 10 codes: C48, C49.0-C49.9 and organ-specific ICD 10 codes (since ICD codes follow the organ of origin). ICD-O-3 topography codes: C47, C48 and C49, ICD-O-3 morphology malignant behaviour codes: 880*, 881*-883*, 884*, 885*-888*, 889*-892*, 893*-899*, 904, 912*-913*, 917*[19, 20]

	MeSH terms: Sarcoma[mh], Soft-Tissue Neoplasms[mh]
Intervention	Regional application of non-invasive external hyperthermia to a STS and administered in addition to chemo- and/or radiotherapy and treatment as usual. Hyperthermia treatment aims to increase the temperature in target tissue to levels above normal systemic temperature. Quality assurance guidelines for regional hyperthermia recognised by the European Society for Hyperthermic Oncology (ESHO) define 40 °C as the temperature at which the treatment starts, while the temperature in the target tissue should not exceed 44 °C.[39, 40] The Kadota Fund International Forum 2004 defines hyperthermia as a modest temperature elevation in the range of 39–45 °C.[41] We accept the treatment temperature to be in the range of 39 to 45 °C according to the guidelines of both ESHO and the Kadota Fund International Forum. We excluded wellness hyperthermia (low-temperature hyperthermia) and ablative (high-temperature hyperthermia) in which tissue is burned. The technology can be described and classified by the anatomical extensiveness of the treated area (local, regional or whole body), by the methods used for hyperthermia application (invasive or non-invasive) and by the energy sources (such as microwaves, radiofrequency, ultrasound, simple radiation) used to provide the intended heating effect.[42] Superficial hyperthermia, whole body hyperthermia and invasive treatment were not included in this assessment. Hyperthermia can be used in both a neoadjuvant context (used before surgical removal of a sarcoma) and in an adjuvant context (used after surgery). In some cases, surgery is difficult or potentially mutilating. This assessment included the use of hyperthermia in both a neoadjuvant and an adjuvant context and in situations in which hyperthermia is used without surgical resection. Product names of the involved technologies for which CE approval was confirmed: BSD 2000 devices produced by Pyrexar Medical, EHY devices produced by Oncotherm, ALBA 4D devices produced byMed-logix srl, Celsius TCS device produced by Celsius 42, Synchrotherm devices produced by Synchrotherm. Devices without CE approval were excluded from this assessment. MeSH terms: Hyperthermia, Induced [mh]
Comparison	Radio- and/or chemotherapy alone in addition to concomitant treatment as usual. We selected the standard interventions for the target population according to clinical guidelines.[43, 44] The main treatment for STS is usually a combination of surgery, chemotherapy and radiotherapy. Radiotherapy and/or chemotherapy can be indicated as pre- or postsurgical (neo-)adjuvant treatment. MeSH terms: Chemotherapy, Adjuvant[mh]; Chemoradiotherapy [mh], Radioimmunotherapy [mh]; Radiotherapy, Adjuvant[mh]; Neoadjuvant Therapy[mh]
Outcomes	The selection of outcomes was informed by the assessment by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA), COMET and the James Lind Alliance.[42, 45, 46] Following the LBI-HTA assessment, overall survival was selected as the main endpoint because it is a clear measure of benefit

	that can be relatively easily obtained, and which is not subject to assessment bias. Additional outcomes included in the LBI-HTA assessment and of interest in this report are disease-free survival, progression-free survival, objective response rate, health-related quality of life, rate of local tumour control and local tumour recurrence and adverse events. Based on the top 10 research priorities formulated by the James Lind Alliance for Living With and Beyond Cancer, we selected the following additional outcomes: pain, fatigue and outcomes related to the psychological well-being of patients, carers and families. For adverse events, the James Lind Alliance research priorities specify an interest in both short-term, long-term (side-effects which last for years after treatment) and late side-effects (side-effects which do not appear until years after treatment). In addition, we included outcomes on amputation, patient satisfaction, procedural time and resource use. Outcomes on patient satisfaction could also include shared decision-making-related measures, which were also included in the top 10 priorities by the James Lind Alliance. We searched the COMET database but did not find a core outcome set specifically for STS. We used the standardised definitions of time-to-event outcomes for sarcomas as these are formulated by the DATECAN initiative.[47] Data from any studies that applied different definitions for time-to-event outcomes would be included, but we would then clearly report any differences in how the outcome was defined. For safety data, we included both adverse events attributed to hyperthermia, but also to those adverse events attributed to the other components or their combinations, as interactions are possible and biological pathways may be unclear, or assumptions of the actual biological pathways may be incorrect. We included outcomes measured at short and long follow-up times. We synthesized the data in categories for a follow-up time, i.e. measured at three months, six months, within one year, one to three years, more than three years after the intervention. We screened the literature to identify any publications on minimal important differences for the outcomes included in this assessment. Summary of included outcomes: Effectiveness outcomes • Overall survival (main endpoint) • Disease-free survival • Disease-specific survival • Progression-free survival • Objective response rate • Health-related quality of life • Rate of local tumour control • Local tumour recurrence • Pain • Fatigue

	• Amputation • Outcomes related to the psychological well-being of patients, carers and families • Motor function • Neurological function Other outcomes • Patient satisfaction (including shared decision-making-related measures) • Resource use Safety • Adverse events (including death related to adverse events, and severe to life-threatening adverse events)
Study design	<u>Effectiveness:</u> Inclusion criteria: Randomised controlled trials and non-randomised prospective controlled trials. We defined the latter as experimental prospective studies in which participants are allocated to different interventions using methods that are not random. In case the certainty of the evidence was rated as very low, low or moderate, we agreed to also include multiple-arm prospective registry studies, provided they were based on data from national, regional or hospital level registries.[48] Exclusion criteria Studies with designs different from the above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health record studies, patient surveys). If suitable evidence syntheses of the above-described studies were available (i.e. Health Technology Assessment (HTA) report, guidelines or systematic review) we planned to use data from such syntheses, plus primary studies published after the last search date of the most recent evidence synthesis. <u>Safety:</u> Inclusion criteria: Randomised controlled trials, non-randomised controlled trials, single-arm trials and single or multiple-arm prospective registry studies based on data from national, regional or hospital-level registries. Exclusion criteria Studies with designs different from the above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health record studies, patient surveys). If suitable evidence syntheses of the above-described studies were available (i.e. HTA report, guidelines or systematic review) we planned to use data from such syntheses, plus primary studies published after the last search date of the most recent evidence synthesis.

Language	We did not apply language restrictions.

1.2 Rating of the importance of outcomes for decision-making

According to the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation), we graded the importance of each outcome through a structured process. Each outcome was rated as critical (score 9–7), important but not critical (score 6–4) or low importance for decision-making (score 3–1).[26] If participants felt that they did not have sufficient information to make a judgement, they were invited to answer "do not know".

In the first round we collected the ratings of the clinical experts. In the second round the members of the assessment team rated the outcomes (one rating/organisation), while using the ratings from the clinical experts as input. While the clinical experts took a clinician perspective, the assessment team took a policy-maker perspective.

We used survey software to collect the individual ratings. This prioritisation of outcomes was conducted in the starting phase of the assessment.

Table 1-1: Rating of the importance of outcomes for decision-making on the use of regional hyperthermia for high-risk STS treatment.

Outcome **EFFECTIVENESS**	**Ratings**		**Final rating**		
	Assessment team (median, range)	**Clinical experts (median, range)**	**Critical**	**Important**	**Not important**
Survival	9 (9–9)	9 (9–9)	●	○	○
Disease-free survival	8 (4–9)	9 (7–9)	●	○	○
Progression-free survival	8 (4–8)	9 (5–9)	●	○	○
Objective response rate	5 (3–8)	6 (3–9)	○	●	○
Health-related quality of life	7 (7–8)	6 (5–6)	●	○	○
Rate of local tumour control	6 (3–7)	6 (5–8)	○	●	○
Local tumour recurrence	6 (3–8)	6 (5–9)	○	●	○
Pain	7 (5–7)	5 (5–8)	●	○	○
Fatigue	6 (2–6)	4 (3–5)	○	●	○
Amputation	8 (7–9)	6 (4–9)	●	○	○
Motor function	6 (5–8)	6 (4–8)	○	●	○
Neurological function	6 (5–8)	5 (4–8)	○	●	○
Psychological well-being of patients	5 (4–6)	4 (4–5)	○	●	○
Psychological well-being of family and carers	3 (1–5)	3 (1–3)	○	○	●
Outcome **SAFETY**	**Ratings**		**Final rating**		
	Assessment team (median, range)	**Clinical experts (median, range)**	**Critical**	**Important**	**Not important**
Mild to moderate AE (grade 1 to 2)	3 (2–7)	2 (1–3)	○	○	●
Severe to life-threatening AE (grade 3 to 4)	8 (7–9)	8 (6–8)	●	○	○

Death related to AE (grade 5)	9 (9–9)	9 (9–9)	●	○	○
Outcome **OTHER**	**Ratings**		**Final rating**		
	Assessment team (median, range)	**Clinical experts (median, range)**	**Critical**	**Important**	**Not important**
Patient satisfaction	6 (3–6)	6 (4–7)	○	●	○
Shared decision-making measures	4 (3–5)	5 (2–7)	○	●	○
Resource use	4 (3–7)	4 (3–5)	○	●	○
Procedural time	3 (2–5)	4 (3-–)	○	○	●

Table A15 in Appendix 4 provides an overview of the individual ratings per outcome.

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

The assessment team organised the tasks as described below:

NIPHNO (author)

- Overall responsibility for production and quality of the assessment.
- Developed the first draft of the project plan.
- Performed the literature search.
- Carried out the assessment: selected and answered assessment elements (for the EFF and SAF domains).
- Coordinated the GRADE process for rating the importance of outcomes for decision-making.
- Completed the checklist on potential “ethical, organisational, patient and social and legal aspects” of the HTA Core Model for rapid REA (relative effectiveness assessment).
- Quality controlled the production process for the TEC and CUR domains.
- Submitted draft versions to reviewers (dedicated reviewers, clinical experts, manufacturers, health organisation) for comments, compiled feedback from reviewers and incorporated relevant changes in the draft.
- Prepared all draft versions and the final assessment including an executive summary.

RER (co-author)

- Reviewed the project plan draft.
- Selected and answered assessment elements for the TEC and CUR domains.
- Contributed to rating the importance of outcomes for decision-making.
- Supported the production of the assessment report and quality controlled all stages of its production (data, information, sources).
- Contributed to answering questions related to potential ethical, organisational, patient and social and legal aspects, if needed.
- Approved/endorsed the conclusions drawn, as well as all draft versions and the final assessment, including the executive summary.

Dedicated reviewers (SNHTA, VASPVT, AETS-ISCIII)

- Thoroughly reviewed the draft project plan and first draft report including studies + results.
- Contributed to rating the importance of outcomes for decision-making.

The clinical experts supported the assessment team by:

- Discussing the project scope with the assessment team.
- Reviewing the project plan.
- Rating the importance of outcomes for decision-making.
- Providing expert advice on the interpretation of the study findings.
- Reviewing the draft assessment.

2.2 Source of assessment elements

We used the HTA Core Model Application for rapid REA (4.2) to select assessment elements.[49] For each selected assessment element, we then formulated a specific research question.

2.3 Search

We used the HTA report by the Ludwig Boltzmann Institute (LBI-HTA) on hyperthermia as a starting point for this assessment.[42] This report was identified through a scoping search for HTA reports by an information specialist at NIPHNO. The LBI-HTA health technology assessment on hyperthermia conducted a systematic literature search from 1990–2012, which we conducted again from 1990 onwards.[42] We opted to do this because of some discrepancies in inclusion criteria for design and some changes in the search filters for study designs. We maintained the same year limit (from 1990 onwards), given the developments in standard oncological therapy.

The search strategy for this assessment was developed by an information specialist at NIPHNO and critically appraised by an information specialist at AETS-ISCIII. The search strategy was based on the population and the intervention in the PICO (Patient, Intervention, Comparison, Outcome). It contained both index terms and text words in order to identify as many relevant studies as possible. The actual information retrieval process was performed by the NIPHNO information specialist and reviewed by the AETS-ISCIII specialist.

As a first step, we looked for relevant systematic reviews, HTAs and guidelines. The use of existing data syntheses prevents duplication of efforts that otherwise would be conducted *de novo* for this assessment. The use of findings of existing evidence syntheses could include use of the results of existing searches and/or use of data extraction, study-level risk of bias assessments, or synthesis.[50, 51] In order to include a synthesis in this assessment, the scope of existing evidence syntheses had to match the scope of this new assessment. Further, we planned for two reviewers to independently appraise the methodological rigour of any relevant evidence syntheses using the AMSTAR2 instrument.[52]

The search for evidence synthesis was conducted on 12 April, 2019 in the following databases:

- Cochrane Library
- Epistemonikos
- Medline (Ovid)
- Embase (Ovid)
- AMED
- HTAi Vortal
- Guidelines International Network (GIN)
- NICE guidance
- NIHR-HTA
- Devices@FDA

We also searched for ongoing and planned systematic reviews in PROSPERO and the POP (Planned and ongoing project) database. No suitable evidence syntheses were found and we therefore conducted a completely new systematic review.

The search for primary studies was conducted on April 16th, 2019 in the following databases:

- Medline (Ovid)
- Embase (Ovid)
- Cochrane Central Register of Controlled Trials
- AMED

We also searched for terminated, unpublished and ongoing primary studies at clinicaltrials.gov and WHO ICTRP.

Appendix 1 includes the detailed search strategy. We did not apply language or publication status restrictions. The reference lists of relevant systematic reviews and included studies were

screened by two people independently. We first screened reference titles and, if potentially included, we followed up with abstract and full-text screening accordingly. We also asked manufacturers of hyperthermia devices to notify us of any published and unpublished (but not confidential) clinical studies/clinical data for their products.

For the TEC and CUR domains, the information from the LBI-HTA report was considered in addition to information from current clinical practice guidelines, information from a general literature search, input from clinical experts and information collected through web searches. The manufacturers were invited to complete the EUnetHTA submission file for the following chapters: 1. Description and technical characteristics of the technology, 2. Health problem and current clinical practice, 3. Current use of the technology, 4. Investments and tools required.

2.4 Study selection

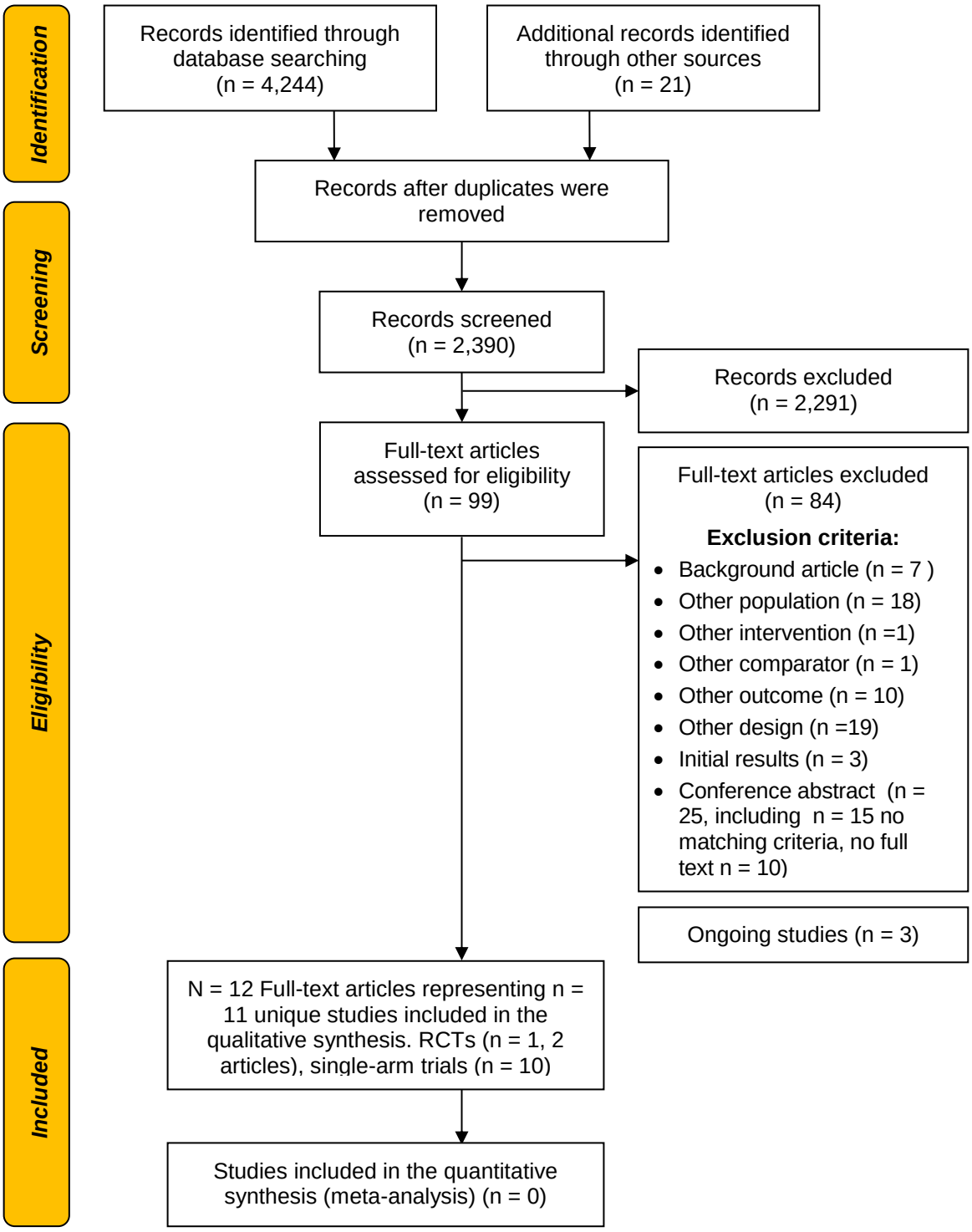


Figure 1: Flow chart

The search for systematic reviews, HTAs and guidelines yielded 1,102 results and a search for primary studies yielded 3,142 results. The screening of reference lists from the included studies resulted in 10 additional references and the manufacturers notified us of a further 11 studies. After removal of duplicates, we ended up with 2,390 references. Two reviewers independently screened studies retrieved through the literature search against the predefined inclusion and exclusion criteria. After screening of titles and abstracts, we excluded 2,291 references. In the

next step, we screened the remaining 99 studies in full text. For potentially relevant conference abstracts we attempted to locate a full text and we contacted the first authors. In cases for which no full text was available, we excluded the study. In cases for which we had studies with initial results and final results, we only selected the final paper(s). Conference abstracts of studies that were available in full text were excluded. The study selection process was double-checked by the co-author team. We included 11 unique studies for analysis. The EORCT study published two papers of the same RCT, one in 2010 and one in 2018.

2.5 Data extraction and analyses

One reviewer used a pre-established form to extract data from the studies, with a detailed revision by another reviewer. We contacted study authors in cases in which we required information that had not been reported in the published paper. Also, for terminated, completed, unpublished and ongoing primary studies we contacted the main investigator(s) listed in the trial registry (information recorded in Appendix 4 Table A15 and the data extraction tables).

We extracted the following data from the included studies:

- Study details: author's name, year of publication, clinical trial identification number, sponsorship source, country, setting, language, declaration of interest, contact with authors.
- Methods: study design, choice of analysis set (e.g. per protocol), characteristics of trial design as outlined in the assessment of risk of bias.
- Population: inclusion criteria, exclusion criteria, total number and number per group, baseline characteristics (age, gender ratio, tumour characteristics, comorbidities). Tumour characteristics including: tumour site (extremity, trunk and retroperitoneal), disease status (primary, recurrent, prior surgery), tumour size, tumour grading, tumour depth, sarcoma histological subtype, WHO performance status, resection status; TNM stage, AJCC prognostic stage group.
- Intervention and comparator characteristics: description of procedure and comparators and concomitant treatments. For hyperthermia we extracted frequency, target, maximum power attained, duration of hyperthermia therapy, temperature variables (max, mean, T90). For radiotherapy we extracted data on type of radiation, dose, number of fractions and total treatment time. For chemotherapy we extracted information on the substances, dose per course, total dose, data on any reduction in doses and on any delays due to side effects.
- Outcome: primary/secondary endpoints as specified in the PICO table above, type, effect measure, scale, number lost to follow-up, follow-up period, treatment discontinuation and reason.

Given that only one RCT (containing two publications) and ten single-arm trials were found, we conducted no meta-analysis. Instead, we provided a descriptive analysis of the data. For the RCT, we reported both relative measures of effect (i.e. relative risk, hazard ratios between pairs of treatments) and absolute effect measures (i.e. absolute risks, risk difference or absolute difference) for each dichotomous outcome. For continuous time-to-event outcomes, we presented the median times and the differences between these medians. For the single-arm trials, we reported the adverse events risk and calculated 95% confidence intervals.

We categorized the safety outcomes into mild to moderate adverse events (grades 1 to 2), severe to life-threatening adverse events (grades 3 to 4), death related to adverse events (grade 5) in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 guide.[53] We preferred to use these terms (instead of minor, major adverse events, deaths) because they provided a more explicit description and were in accordance with the CTCAE framework. For studies that provided no CTCAE grades, the clinical experts assigned CTCAE grades if sufficient descriptive information was available.

While we intended to distinguish between acute and late toxicity, we found that this was poorly reported in the included studies. Further, there was insufficient information available to make confident assessments of what could have been an acute or a late toxicity. Thus, we only reported on acute or late toxicity if this was clearly mentioned in the included studies, together with a description of the reasonable interpretation of acute/late toxicities in the discussion section.

We presented the data in the way they had been analysed by the authors, i.e. as intention-to-treat (ITT), as-treated or per-protocol. If the authors stated the number of adverse events as counts, without reference to the denominator, we calculated the risk, assuming an ITT.

In order to interpret the magnitude of effect sizes we have screened the literature to identify accepted standards for minimal important differences for the outcomes that we selected in this assessment. Within this context we identified the clinically meaningful outcomes for cancer trials defined by the American Society of Clinical Oncology (ASCO).[27] However, these minimal important differences goals are disease-specific and are defined for carcinomas of the pancreas, breast, lung and colon. We did not find any agreed minimal important differences for sarcoma patients. The outcome for sarcoma tumours is generally more favourable compared to the cancer types addressed by ASCO. We therefore considered these to be reasonable minimal requirements. We summarized the ASCO working group set thresholds as follows: hazard ratio for overall survival of 0.8 or less, a minimum 25% increase in median overall survival, and a minimum 3-month improvement in progression-free survival. These goals were chosen by ASCO as modest and attainable thresholds.

2.6 Quality rating

For RCTs, two reviewers independently appraised the risk of bias on study and outcome level using the Cochrane Risk of Bias tool.[24] For non-randomised studies (including the single-arm trials), we used the ROBINS-I tool (Risk of Bias in non-randomized studies – of interventions).[25] Any disagreements were resolved by discussion. We included studies with both low, high and unclear risk of bias.

For RCTs and non-randomised studies, if an individual domain was high risk/serious, the overall judgement of the risk of bias meant that the study as a whole had a risk of bias that was at least this severe. Thus, a judgement of “high” risk or “serious” bias within any given domain had similar implications for the study as a whole, irrespective of which domain was being assessed.

We planned to perform sensitivity analyses according to the different risk-of-bias categories, but excluded this because a meta-analysis was not applicable.

To rate the certainty of the evidence for each outcome, we used GRADE. For each outcome, we took into account the risk of bias, imprecision, inconsistency, indirectness and publication bias.

We expressed certainty as high, moderate, low or very low as defined by the GRADE working group.[26]

For the TEC and CUR domains, no quality tool was used. Clinical experts and manufacturers reviewed the descriptions provided below.

2.7 Patient involvement

We aimed to involve patients during the scoping phase in order to capture their experiences and views of the disease and intervention being assessed. We invited a patient/consumer representative group from Norway and a European patient group. We also published an open call for patient involvement on the EUnetHTA website, which was combined with an invitation to European umbrella organisations. Unfortunately, we had a low response to the invitations and were unable to involve patients.

2.8 Description of the evidence used

Table 2-1: Main characteristics of the included studies

Author and year or study name	Study type	Number of patients at baseline	Interventions	Main endpoints	Included in clinical effectiveness and/ or safety domain
EORTC trial [28, 29]	RCT	341, (169 versus 172)	>Neoadjuvant: C + RH >Surgery and/or R >Adjuvant: C + RH	Overall survival Disease-specific survival Local progression-free survival Disease-free survival Amputation Objective response rate Adverse events (C+RH-related only)	EFF SAF
Hayashi 2015[31]	Single-arm trial	6	>Neoadjuvant: R + RH + C >Surgery >Adjuvant (unplanned): C (for 5 patients)	Adverse events (C+R+ RH-related only)	SAF
Fiegl 2004[54]	Single-arm trial	20	Neoadjuvant C + RH	Adverse events (for treatment overall)	SAF
Baur 2003[55]	Single-arm trial	19	Neoadjuvant: C + RH	Adverse events (limited to prespecified events)	SAF

Author and year or study name	Study type	Number of patients at baseline	Interventions	Main endpoints	Included in clinical effectiveness and/ or safety domain
Wendtner 2001[56]	Single-arm trial	54	>Neoadjuvant: C + RH >Surgery >Adjuvant (for patients without progressive disease): C + R (not for pre-irradiated patients)	Adverse events (for treatment overall)	SAF
Issels 2001[57]	Single-arm trial	59	>Neoadjuvant: C + RH >Surgery >Adjuvant: C + RH + R (for non-preradiated patients)	Adverse events (neoadjuvant C + RH only)	SAF
Maguire 2001[58]	Single-arm trial	35	>Neoadjuvant: R + RH >Surgery	Adverse events (RH related only)	SAF
Prosnitz 1999[30]	Single-arm trial	97	>Neoadjuvant: R + RH, >Surgery >Adjuvant (unplanned): C for 8 patients	Adverse events (for treatment overall)	SAF
Makihata 1997[59]	Single-arm trial	14	>Neoadjuvant: R and/or C + RH >Surgery	Adverse events (for RH and surgery only)	SAF
Uno 1995[60]	Single-arm trial	8	C + R + RH Palliative care	Adverse events (for treatment overall)	SAF
Volovat 2014[61]	Single-arm trial	24	C + RH Palliative care	Adverse events (for treatment overall)	SAF

Abbreviations: EFF= effectiveness, SAF= safety, RH= regional hyperthermia, C=chemotherapy, R= radiotherapy

2.9 Deviations from the project plan

During the screening process, we observed that many subgroup analyses had been published for the EORTC trial. These subgroup analyses were of an exploratory nature without prespecified hypotheses and a large number of factors were being tested. The availability of prespecified hypotheses that are limited to a small number of tested factors are considered to be critical requirements for credible subgroup analyses. We therefore decided not to include these.[62]

We incorporated disease-specific survival outcome following changes from EORTC from 2010 to 2018. While rating the outcomes it was decided that motor function and neurological function should be added as outcomes of interest.

Upon completion of the first draft of the assessment report, we identified the need to obtain feedback from an oncological surgeon. We invited an expert with this profile, who then provided input on the second draft.

Based on feedback on the second draft from a manufacturer, we added additional device terms to the search string.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications have different types of regional hyperthermia devices received marketing authorisation or CE marking?
B0002	What are the claimed benefits of regional hyperthermia in relation to the comparators?
B0003	At what phase of development and implementation are regional hyperthermia devices in the treatment of STS and the comparators?
B0004	Who administers regional hyperthermia and the comparators and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use regional hyperthermia and the comparators?
B0009	What equipment and supplies are needed to use regional hyperthermia and the comparators?
A0021	What is the reimbursement status of regional hyperthermia in the different EU countries?

3.2 Results

Features of the technology and the comparators

[B0001] – What are the technology and the comparator(s)?

The technology under assessment is regional hyperthermia added to conventional therapies to treat high-risk STS.

Conventional therapies for STS

STS are a rare and heterogeneous group of tumours, which occur in connective tissues embryologically derived from the mesenchyme.[63] There are approximately a hundred of unique subtypes of sarcoma, each sub-term typically indicating the tissue type that the tumour morphology resembles.[64] Most sarcomas develop in muscles, blood vessels, nerves, fat or other soft tissues of the body, and are known as STSs.

Surgery remains the mainstay of treatment and is a prerequisite for curing most types of STS, supported by advanced multimodal therapies.[1] Decisions about optimal surgical procedure for the primary tumour are based on different aspects: tumour histology, location, tumour size, involvement of adjacent anatomical structures, patient preference, age and general medical condition, as well as response to neoadjuvant therapies.[63] The primary aim of curative surgery is to

excise the whole tumour with tumour-wide margins that ensure a safety cuff of healthy tissue surrounding the entire circumference of the tumour in order to remove infiltrative extensions and ensure no cancer cells remain.[65] Staging of the local tumour is essential for surgical planning.[66] Imaging of the affected site should include plain X-ray radiographs, CT, PET or MRI.[21] The tumour size, capsule, consistency, site, shape, edge and adjacent structures are vital pieces of information for planning the surgical margins and reconstructions after assessing the response to neoadjuvant therapies.[63] Sarcomas have a predilection to grow centrifugally, pushing the surrounding tissue aside as they grow. During this process, a pseudocapsule of compressed tissue and inflammation develops around the tumour, which often contains micro-satellites of tumour tissue. Sarcomas commonly occur intra-compartmentally (one anatomic compartment) and become extra-compartmental once they grow to a size that exceeds the confines of the original compartment.

Different classification systems are available for surgical margins. According to the Enneking classification, [65, 67] which is mainly based on macroscopic findings during surgery and is particularly applicable to STSs of the extremity and trunk wall, there are four primary forms of surgical margins in sarcoma surgery: intralesional (excision of tumour with microscopic disease remaining and potentially macroscopic disease), marginal (excision of tumour from within the surrounding reactive zone; no adjacent structures are excised), wide (the entire tumour is excised with a border of normal tissue encasing 100% of the tumour's margins) and radical (this form indicates an extra-compartmental excision involving all compartments that contain tumours).[2, 68] This classification has become popular for its practical utility in surgical planning, but reproducibility may be an issue.[69]

The R classification, based on both the macroscopic and microscopic assessment of the resection margins, is increasingly used because the definition of margins is clear and easily understandable. The margin is categorized either as grossly positive (R2), microscopically positive (R1) or microscopically negative (R0).[70]

Patients with STSs are at risk of developing local recurrence and distant metastasis despite surgical tumour resection. To try to address this crucial issue, a multidisciplinary approach based on surgery, radiotherapy and/or chemotherapy has been applied.[2, 71] Sometimes, chemotherapy, radiation, or both, may be given before surgery.[3, 4] This neoadjuvant treatment approach can be used to shrink the tumour so that it can be removed completely, or to treat high-grade sarcomas when there is a high risk of the cancer spreading. Chemotherapy and/or radiation may also be used after surgery. In such cases, the goal of adjuvant treatment is to kill any cancer cells that may remain in the body in order to lower the risk of the cancer returning. In addition to radiotherapy, chemotherapy delivered concurrently with radiotherapy has been investigated as a mechanism for improving resectability.

Radiation therapy uses high-energy rays (such as x-rays) or particles (electrons, protons, heavy ions) to kill cancer cells. Radiation can be the main treatment for sarcomas in someone who is not healthy enough to undergo surgery. Radiation therapy can also be used to help ease sarcoma symptoms with a palliative intent when it has spread. External beam radiation is the most commonly used treatment for sarcomas.[5] Treatments are generally given daily, five days a week, usually for several weeks. In most cases, a technique called intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) is used. This better focuses the radiation on the cancer areas and lessens the damage to the surrounding healthy tissue. Proton beam radiation that uses streams of protons instead of x-ray beams – although possessing a number of advantages over IMRT – is not yet widely used as proton beam therapy is not generally available. Intraoperative radiation therapy (IORT) is given in the operating room after the tumour has been

removed but before the wound is closed, using a single fraction of radiation.[72, 73] Giving radiation this way means that it doesn't have to travel through healthy tissue to reach the area that needs to be treated. It also allows adjacent healthy areas to be shielded more easily from the radiation.[74] Often, IORT is only one part of radiation therapy and the patient will receive some other type of radiation after surgery. Sometimes, brachytherapy treatment is applied in which pellets (or seeds) of radioactive material are placed in or near the cancer. For STSs, these pellets are inserted into catheters (very thin, soft tubes) that have been placed during surgery. Brachytherapy may be the only form of radiation therapy used or it can be combined with external beam radiation.[75]

Chemotherapy is the use of drugs administered into a vein or taken orally to treat cancer. These drugs reach all areas of the body, making this treatment useful for cancer that has spread (metastasized) to other organs. Depending on the type and stage of sarcoma, chemotherapy may be given as the main treatment or as an adjuvant (addition) to surgery.[6] Different types of sarcomas respond better to chemotherapy than others and also respond to different types of chemotherapy. A combination of several anti-cancer drugs is generally used in STS.

The most common drug is doxorubicin (Adriamycin). It is usually given alone as standard first-line chemotherapy. Ifosfamide (Ifex) is used alone or in combination with doxorubicin. Mesna (Uromitexan) is given at the same time as Ifosfamide. It is a supportive drug used to protect the bladder from damage and lower the risk of urinary tract problems caused by the chemotherapy. If a STS does not respond to drugs used in earlier treatments or if it returns, other chemotherapy drugs may be used. Chemotherapy for a STS is most often given through a needle into a vein (intravenously). It is usually given for a few days every three weeks. How often and how long chemotherapy is given depends on the type of drug or drug combination used. It is usually given for several months.

Targeted therapy is also used since some specific types of STSs appear to be more sensitive to certain drugs. Targeted therapy uses drugs or other substances to identify and attack sarcoma cells while causing minimal damage to normal cells. These therapies attack parts of cancer cells that make them different from normal, healthy cells.[7] Each type of targeted therapy works differently, but all of them affect the way a cancer cell grows, divides, repairs itself or interacts with other cells. Targeted therapy is an important part of treatment for many kinds of cancer, while for sarcomas it is still at an early-stage treatment modality.

Hyperthermia

Hyperthermia (HT) is usually taken to mean a body temperature that is higher than normal.[8, 9] The carefully controlled use of heat for medical purposes can be applied to treat cancer. Tissue absorption of electromagnetic energy causes heating by molecular excitation. Living tissue dissipates accumulated thermal energy principally through transport by blood perfusing the tissue. Solid malignant tumours of significant size have less blood perfusion than the surrounding normal tissue. For a given absorbed thermal dose, usually expressed as the number of equivalent minutes at a certain temperature (generally 43°C),[76] the reduced ability to dissipate heat causes tumour tissue to reach higher temperatures than normal tissue. Thus, the absorbed electromagnetic radiation will preferentially heat tumours present in normal tissue and cause them to reach higher temperatures than the normal surrounding tissue. When cells in the body are exposed to higher than normal temperatures, changes take place inside the cells. These changes can make the cells more likely to be affected by other treatments such as chemotherapy or radiation therapy.[10, 11]

Hyperthermia used in combination with chemotherapy is expected to increase the drug concentration in the tumour region due to the increased blood flow and to raise the effectiveness of cytostatic drugs.[77] In addition, hyperthermia has been proven to enhance drug toxicity in cells that are resistant to many drugs. Thus, there is a rationale to employ hyperthermia synergistically with chemotherapy in strategies for treating high-risk tumours.

The addition of hyperthermia to radiotherapy could improve the efficacy of the treatment.[78] This is because the temperatures attained through hyperthermia increase blood flow to the tumour, accentuating the formation of the oxygen radicals required to attack cancer cell DNA through radiotherapy.[79] Heat shock through hyperthermia may also inhibit DNA repair in cancer cells after double-strand breaks occur as a result of ionizing radiation. Furthermore, hyperthermia may kill radiation-resistant hypoxic cancer cells by forcing a rise in anaerobic metabolism, causing the cells to weaken as their energy supply is depleted and the become toxically acidic as their consumption exceeds their ability to expel waste.

Regional hyperthermia

Hyperthermia treatments can be local, regional (superficial and deep) or whole body depending on the extent of the area being treated.[8] In regional hyperthermia a part of the body, such as an organ, limb or body cavity (a hollow space within the body) is heated. The (ESHO) quality assurance guidelines specify that in regional hyperthermia the temperature of the target is increased in the range of 40–44 °C and that measuring temperature is of great significance.[39]

Superficial hyperthermia is used for superficial, locally limited and advanced tumours, for example, skin cancer, recurring breast cancer or inoperable head and neck tumours [80]. In general, superficial hyperthermia is applied to tumours that infiltrate up to 4 cm into the tissue. The type and position of the tumour determines the choice of applicator. Small soft-tissue tumours (breast, prostate, etc.) are easily treated with multiple antenna needles (interstitial hyperthermia, see Fig. 7) that are placed in suitable percutaneous catheters.[81] Depending on tumour size, multiple antennas can be used, and separate temperature sensors placed parallel to the needle antenna measure the temperature. Applicators of different sizes are placed on subcutaneous tumours and a water bolus (a special bag filled with liquid, see Fig. 4) is used to transfer energy to the patient.

Deep hyperthermia, on the other hand, is used to supply therapeutic heat to those tumours that are located more than 3–5 cm below the skin surface.[82] Here, the tumour region is heated to the desired temperature using targeted electromagnetic energy (radio frequency). Antenna arrays, mounted in applicators of varying shapes and placed around the body, focus this energy onto specific tumour locations. The amplitude and phase of the radio frequency (RF) energy can be adjusted to provide the most suitable heating pattern for the individual tumour shape and size. With deep hyperthermia, patients lie inside dedicated applicators. In some systems, a water bolus and antennas that radiate high-frequency electromagnetic waves are present and integrated into the applicator. Other systems use a water bolus that is not integrated into the applicators but positioned between antennas and patient.

These waves can be focused on the tumour via the independent control of individual antennas and lead to regional heating. The treatment region can be heated to targeted therapeutic temperatures of 41°C up to 44°C. To achieve the therapeutic temperatures while protecting the surrounding tissue, it is necessary to use special applicators with suitable control systems.

Regional hyperthermia for STS

Regional hyperthermia is always applied in addition to radiotherapy or chemotherapy, or both, but is not effective as a single treatment.[12-14] There is no consensus on the optimal application mode for hyperthermia. The combination with chemotherapy varies according to the drug used. Chemotherapy and hyperthermia can be concomitant or sequential (first chemotherapy, time variable with the drug). For the neoadjuvant setting, regional hyperthermia in combination with a doxorubicin- and ifosfamide-based chemotherapy is supposed to improve the tumour response rate and to better prevent early disease progression compared to chemotherapy alone. The addition of regional hyperthermia to a multimodal treatment of high-risk sarcoma treatment comprising surgery, radiotherapy and chemotherapy, either in the neoadjuvant setting, as well as after incomplete or marginal tumour resection, is supposed to improve local recurrence- and disease-free survival. Based on these claims, in conjunction with its supposed low toxicity, regional HT combined with preoperative or postoperative chemotherapy is proposed as an additional standard treatment option for the multidisciplinary treatment of locally advanced high-grade sarcoma.

Isolated limb perfusion is a specific technique that can be used for regional hyperthermia in the management of STS of the extremities. It involves surgical isolation of the vascular inflow and outflow of an extremity in order to separate the circulation of the affected limb from that of the remainder of the body, leading to high concentrations of drugs in the perfused limb without exposing the rest of the body to the same level of toxicity. The isolated extremity can then be subjected to mild hyperthermia to improve the antitumour effect. Isolated limb perfusion appears to provide the opportunity to salvage limbs that might otherwise require amputation because of a locally advanced or recurrent tumour. However, no randomized trials comparing this technique with other treatments are available, and the quality of the available studies is limited, showing significant methodological heterogeneity.[83]

Regional hyperthermia technologies

Radio waves, microwaves, ultrasound waves and other forms of energy can be used to heat the tumour area, although radiofrequency hyperthermia devices are most used in commercial systems.[15, 16, 84] Radiofrequency hyperthermia devices can be categorised as radiative and capacitive technologies.[9, 16] Capacitive systems were primarily used at first as they are more affordable and easier to use than radiative systems. Capacitive heating applies electrodes with an integrated water bolus bag. Additional boluses (overlay boluses) can be used for more aggressive skin cooling. The patient will typically lie on a treatment table with an embedded electrode and integrated water bolus. Another electrode (with integrated water bolus) is positioned on the patient and the resulting currents produced by capacitive coupling with the body cause heating. When equally-sized electrodes are used, the absorbed power is directed towards the centre of the distance between the electrodes. When different sizes of electrodes are combined, the power distribution is directed to the side of the smallest electrode. Thus, for eccentric tumours, the diameters are usually different, with the smallest electrode closest to the tumour location. The EHY models (OncoTherm kft), Celsius TCS (Celsius42 gmbH), and RF 1200 S (SynchroTherm) are capacitive systems operating at 13.56 MHz. The characteristics of regional hyperthermia technologies are described in Table 3-1.

Radiative external antennas induce an electromagnetic field that is coupled to the patient using a water bolus.[85] Adequate target heating can be realised by using phase and amplitude steering to create constructive interference among the electromagnetic fields radiated by the individual antennas. In phased array systems, by varying the power of each applicator (amplitude and phase), it is possible to create different interference patterns of the fields generated in order to focus the electromagnetic energy in the target volume and generate a temperature increase of the latter in

the 40 –44 °C range, which must be maintained for 60 minutes. By varying the power of each applicator, the intensity of the emitted radiation is changed and, consequently, the temperatures reached: as the power increases, the temperature increases. By varying the phases of each applicator with respect to the one assumed as reference, the position of the focus is changed. Radiative heating systems typically operate in the frequency range between 70 and 120 MHz. Commercial radiative loco-regional systems are the BSD-2000 (Pyrexar Medical) [16] and the ALBA 4D (ALBA Hyperthermia System).[16]

Both capacitive and electromagnetic radiative hyperthermia systems are used for superficial heating.[86] Examples of superficial capacitive systems are OncoTherm (OncoTherm kft) and Celsius TCS (Celsius42 gmbH) operating at a frequency of 13.56 MHz. During capacitive heating, the patient lies on a treatment table with an embedded electrode and integrated water bolus bag. Another electrode is positioned on the patient and the heating of the tumour is caused by the resulting currents produced by the capacitive thermodynamic effects. If radiative superficial systems are used instead, radiative antennas induce an electromagnetic field that is coupled to the patient using a water bolus. BSD-500 (Pyrexar Medical) and ALBA ON4000 (ALBA Hyperthermia System) are among these commercial systems. These radiative systems have an operating frequency of 434 or 915 MHz. Their position is in contact with the treatment area.[86] See Table 3.1.

Side effects of regional hyperthermia

Since regional hyperthermia is often given with other cancer treatments such as chemotherapy and radiation, the side effects of these treatments may be seen at different intervals.[8] Experience, improved technology and improved skills in using hyperthermia treatment have resulted in fewer side effects. Hyperthermia has the potential to produce a variety of adverse effects and those regularly observed during clinical studies are related to the direct effects of heat on tissue and indirect effects related to the tumour, including burns, pain, ulceration and infection .[87]

General warning regarding hyperthermia treatments

Because the patient's ability to detect pain is an essential safety mechanism, hyperthermia is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, regional or general anaesthetic, or other condition) (Indications that are reported in the user manuals of the hyperthermia equipment described in this report, n.d.). Since excessive heating of normal tissue is prevented by normal blood perfusion, it is important that adequate circulation is present and maintained in all tissues within the heating field.

The electromagnetic energy from microwave applicators may interfere with cardiac pacemakers or other implanted electronic devices. Large thermal doses (a continued elevation of moderately high temperature or a short extreme elevation of temperature) in normal tissues situated in the vicinity of the treated tumour or between the tumour and the body surface may result in regions of thermal aseptic necrosis that require medical intervention and that may not be apparent on inspection of the skin.

Treatment of tumours located in the neck and head may cause inadvertent heating of thermoregulatory centres located in the brain stem and induce a general thermoregulatory response that exceeds the patient's compensatory capabilities.

Table 3-1: Features of the intervention

	Technology								
Model	EHY 3010 ML	EHY 2000 Plus	EHY 2030	Celsius TCS	RF 1200 S	ALBA ON 4000	ALBA 4D	BSD 500 (previously BSD1000)	BSD2000 3D/MR
Manufacturer	OncoTherm Kft.			Celsius42 GmbH	SynchroTherm	ALBA Hyperthermia System		Pyrexar Medical International	
Headquarter	Budaörs, Hungary			Eschweiler, Germany	Rome, Italy	Rome, Italy		Salt Lake City, UT 84119, USA	
Names in other countries	OncoTherm GmbH, Troisdorf, Germany / OncoTherm Ltd., LLC, 1942, Boulder CO 80302, United States			----	----	ALBA - MedLogix, Rome, Italy		Dr. Sennewald Medizintechnik GmbH, München, Germany	
WEB Page	www.oncotherm.com			www.celsius42.de	www.synchrotherm.com	www.albahyperthermia.com		www.pyrexar.com/ www.sennewald.de	

Reasons for choosing the above technology:

Many companies supply equipment for superficial and deep hyperthermia [www.globenewswire.com, “Deep Hyperthermia Device Market, Global Future - Emerging Growth Prospects by 2025”] that are applied to the treatment of different oncological diseases. Here is a non-exhaustive list of companies that develop systems for deep hyperthermia: ALBA Hyperthermia System, Andromedic, BoHua Medical, Celsius42, Hunan Huayuan Medical Device Co., Hunan Unimed, Jilin Orestep Medical Equipment, Nanjing Greathope, Nova Company, Oncotherm, OrienTech, Perseon, Pyrexar Medical, Shanghai Huayuan, Vinita, Xianke Medical Equipment. Contacting all these companies would be beyond the scope of this report, which is to make a technical comparison of the various systems on the market. Thus, EUnetHTA has selected a number of these companies in order to describe the different types of technologies used on STSs. The systems presented have been identified considering indicators, chosen in a totally discretionary manner, among which include the level of company diffusion in the European Union, system citations in the scientific literature that is analysed in this report, the type of products offered and their presence on the website of the European Society for Hyperthermic Oncology (ESHO).

We present a technical overview of regional hyperthermia systems, shown in Table 3.1, for treating STS. For the technological description, either the technical questionnaires supplied by the companies (the Submission files) to EUnetHTA or the technical sheets on their websites have been considered. All images of the hyperthermia systems presented and described below have been extracted from the websites of the companies.

OncoTherm

Figure 2. EHY 2000, 2030 & 3010ML systems [87]

EHY 2000

EHY 2030

EHY 3010ML

OncoTherm devices are based on the traditional hyperthermia concept.[88-90] According to the claims on the manufacturer's website, these devices focus selectively on the tumour cells instead of isothermal focusing on the tumour area. This is achieved by applying a modulated high frequency electrical current through the target area, which selects and attacks the tumourous cells, based on their biophysical differences from their healthy counterparts. All the EHY systems with a special radio frequency generator are capacitive hyperthermia devices for the treatment of superficial and deep solid tumours. The principle of operation is based on the use of a single applicator (available in different sizes) that must be positioned on the target area, while a counter electrode is attached to the treatment bed. The operating frequency of all the systems is 13.56 MHz with a maximum radiated power between 150 W and 600 W. In EHY2000, the changeable applicator uses conventional bolus cooling, which keeps the surface temperature in the homeostatic range. In EHY2030 and EHY3010ML, the radiating elements (electrode types) are composed of a metallised textile with a temperature-controlled bolus in which distilled water circulates for thermoregulation.

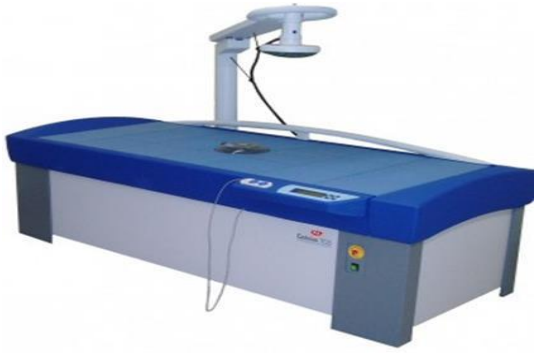
In EHY-2030, a new mechanical arm has been introduced that was designed to provide a better reach more conveniently. The diameters of the two possible electrode variants are 20 cm (150 W max) and 30 cm 250 W max). Systems for monitoring patient temperature are not described. Temperature measurements are available using the TM200 and TM300 devices developed by Oncotherm for sensing temperature under RF power. It is widely used in experiential applications but has not yet been approved for clinical use.

The radiating elements (electrode types) are composed of a metallized textile with a temperature-controlled bolus in which distilled water circulates for thermoregulation. The diameters of the two possible electrode variants are 20 cm (150 W max) and 30 cm (250 W max). Systems for monitoring patient temperature are not described.

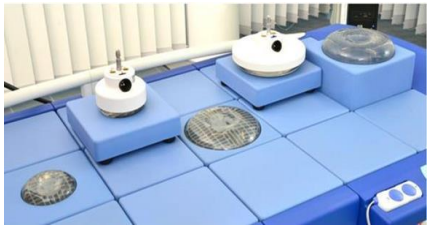
All the devices have a digital operation station. None of these systems require room shielding or an extra room.

Celsius42 GmbH

Figure 3. Celsius TCS [87]



Celsius TCS



Set of electrodes (of Celsius TCS)

The Celsius TCS is a capacitive hyperthermia device system for the treatment of superficial and deep solid tumours. Electromagnetic currents and heat are generated by capacitive thermodynamic effects in the tissue. The principle of operation is based on the use of a single applicator that must be positioned on the target area. The operating frequency of the system is 13.56 MHz with a maximum radiated power of 500 W. The system can be used to locally induce

temperatures greater than 40°C. With its safety concept (hand switch for patient to interrupt the treatment session, redundant power monitoring, etc.), the system can currently apply radiated power of up to 350 W. The system is designed for a power output of up to 600 W.

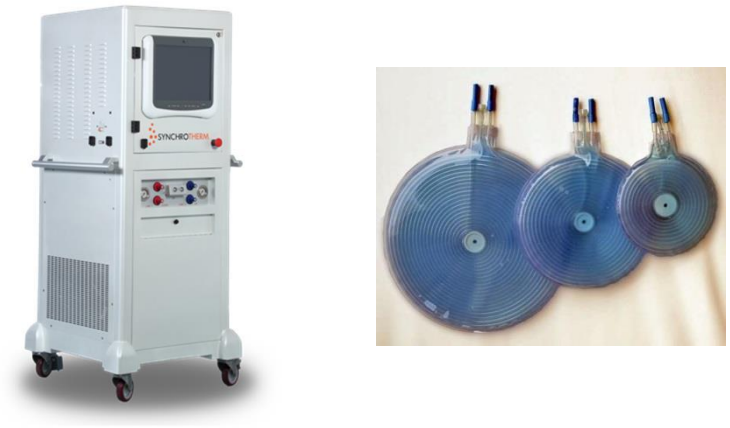
Electrodes available for use with the Celsius TCS System comprise two different arm electrodes and three different tile electrodes with diameters ranging from 15 cm to 25 cm. Within the electrodes are metal plates that are electrically connected to the radio frequency generator. All components that come into contact with the skin are made of biocompatible material. By choosing appropriate electrodes, all active cooled, the focus of the energy input can be precisely adapted to the treatment situation. In simple terms, the human body equivalent circuit can be described as a capacitor, consisting of the volume that is filled with an RF current between the electrodes, and the associated effective surface at the electrodes.

The electrode design is intended to minimize the risk of operating errors and, thus, of burn injuries. At high power outputs in particular, there is an integrated feedback system that permits the patient to interrupt the treatment session at any time, preventing potential burn injuries. A temperature measuring device for use in the high frequency field is currently undergoing approval testing. It will be employed to monitor treatment quality when needed.

The device has a digital operation station. This system does not require room shielding or an extra room.

SyncroTherm

Figure 4. RF 1200 S (technical documentation available on the company's website).



RF 1200S	RF 1200 S applicators and bolus of different sizes

The RF 1200S is a capacitive hyperthermia device system for the treatment of deep solid tumours. Electromagnetic currents and heat are generated by capacitive thermodynamic effects in the tissue. The principle of operation is based on the use of applicators that must be positioned on the target area. The operating frequency of the system is 13.56 MHz with a maximum radiated power of 600 W (continuous), 1200 W (random modulated) or 2400 W (pulsed, Pulsar System). In this last example, two generators are used.

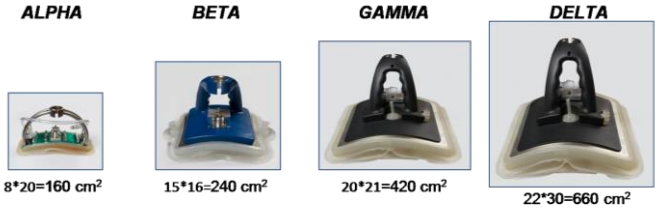
The system can be used to locally induce temperatures greater than 40°C. Deformable antennas (diameters of 12 cm, 18 cm and 26 cm) are used to adapt to the anatomical parts of the patient and promote a uniform electromagnetic field, coupled with a better focal radiation concentration. Pressurized refrigeration bags (diameters of 17 cm, 23 cm and 31 cm) with a constant thickness for uniform surface temperature are used. Independent regulation of temperature in the single lines optimizes the tolerability and safety of the treatment, reducing the possibility of burns considering the delivery of high power. Range of accessories are available for the treatment of chest, abdomen, pelvis, head and limbs that can be applied even to difficult areas such as the neck, mouth, armpit, inguinal cord. Systems for monitoring patient temperature are not described.

The device has a digital operation station. None of these systems require room shielding or an extra room.

ALBA - MedLogix Hyperthermia Systems

Figure 5. AlbaON 4000 [87]

ALBA ON 4000



ALBA ON 4000 applicators of different sizes

The Alba On4000 is a radiative hyperthermia system for the treatment of superficial and semi-deep solid tumours. The principle of operation is based on the use of a single applicator (available in different sizes) that must be positioned on the target area. The operating frequency of the system is 434 MHz with a maximum radiated power of 200 W. The radiating elements are composed of contact curved micro-strip applicators, curved antennas that have optimal adaptability to the geometry of the anatomical area to be treated. The maximum heating depth is 4 cm and the temperature reached by tissues is in the range of 40°C–45°C. The temperature is measured for the entire duration of the treatment by means of probes placed on the skin or interstitially (if required). The water bolus for the energy transmission is filled with circulating distilled water for both signal and superficial thermoregulation. The system is equipped with four antennas of varying effective field size (the area enclosed within 50% of SAR [specific absorption rate] at a depth of 1 cm) in a range between 64 cm^2 and 440 cm^2. The thermometric system can have up to 32 channels.

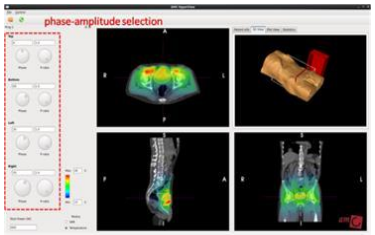
It is also possible to extend the ALBA On4000 with a second unit permitting the simultaneous use of two applicators of the same or different size to treat two lesions at the same time, or very large tumours. The device has a remote operation station and can be integrated into an ultrasound system for tumour visualization, applicator positioning and eco-guided insertion of temperature sensors.

In Europe, the Middle East and Africa (EMEA), the system does not require room shielding because a frequency of 434 MHz is not the industrial, scientific and medical radio band (ISM) in such regions.

Figure 6 ALBA 4D [87]

ALBA 4D

ALBA 4D Superficial cooling system (bolus)



ALBA 4D Treatment planning system

The ALBA 4D is a radiative hyperthermia system for the treatment of deep solid tumours. The operating frequency of the system is 70 MHz with a maximum radiated power of 2000 W. The ALBA 4D is a phase-controlled system consisting of an array of four antennas, waveguide applicators independently controlled both in amplitude and phase. Varying these parameters permits a spatial shift of the radiated electromagnetic fields in order to focus the energy at depth on the target according to its geometry and location in the patient. The ALBA 4D automatically records antenna/gantry positions. The temperature reached in tissues generated by heating is in the range of 40°C–45°C. The temperature is measured for the entire duration of the treatment by means of probes placed in the patient. The system, which is movable via a remote keyboard, can be adapted to treat different-sized patients, from paediatric patients to robust adult patients. This is due to the three antennas positioned on the gantry which, being movable and robotized, can be easily and quickly adapted to different-sized patients.

The ALBA 4D also has a thermo-regulated water bolus to protect superficial tissue and permit optimal radio-frequency coupling. The water bolus, filled with circulating distilled water, both for signal coupling and superficial cooling, has been designed to improve patient comfort. Due to the different bolus sizes to be used according to the patient size, it is possible to maintain a distance of only 5 cm between the antennas and the patient. This is intended to permit optimal electromagnetic coupling and low water weight to be supported by the patient during the 1-hour treatment. The gantry, as a whole, is also robotized and moves vertically. The ALBA 4D is equipped with a dedicated patient positioning system, a solid patient bad and a laser pointing system that permits accurate target positioning within the array. Thus, 3D steering is not required. The ALBA 4D has motorized movement and its thermometric system comprises 56 temperature

sensors arranged in multi-tip probes for real-time in-vivo dosimetry. In addition, special devices called pelotte" are available to support temperature and electro-magnetic-field probes in the natural cavities (vagina and rectum) of the pelvic region.

A new element of ALBA 4D is the RF signal measuring device (DET, "detector") that is integrated into the signal generator (DDS / DET) that measures the power and phase of the forward and reflected signals, together with specifically designed tracking algorithms, allowing a feedback control to counteract and rectify any phase or power drift in real time during the treatment.

The ALBA 4D has a treatment planning system (HTPS) for optimal patient-specific settings and on-line adaptive planning.[10, 11] The HTPS can actually re-calculate temperature and SAR distribution via its settings change – instantaneously and in real time.

The system requires room shielding because a frequency of 70 MHz is not an ISM radio band in such areas.

Pyrexar Medical Inc.

BSD 500 (technical documentation and technical brochures downloaded from the company's website, we sought permission to use device images, but received no response from the manufacturer).[91]

The BSD 500, which replaced the BSD 1000 in 2003, is a system for the treatment of superficial solid tumours. The principle of operation is based on the use of a single applicator (available in different sizes) that must be positioned on the target area. The operating frequency of the system is 915 MHz with a maximum radiated power of 250 W. The radiating elements are composed of waveguide antennas. The maximum heating depth is 2.5 cm and the temperature reached by tissues is in the range of 40°C–45°C. The temperature is measured for the entire duration of the treatment through probes placed on the skin or interstitially (if required). The water bolus for the energy transmission is filled with circulating distilled water for both signal and superficial thermoregulation. The system is equipped with four antennas of different effective field size (the area enclosed within the 50% of SAR at a depth of 1 cm) in the range between 6.25 cm^2 and 156.25 cm^2. The thermometric system can have up to eight channels. The device has a remote console.

The BSD 500 hyperthermia system induces therapeutic heat (hyperthermia) through the external or interstitial application of electromagnetic energy. The interstitial antennas can be used in conjunction with the HDR brachytherapy applicators. The semi-rigid MA-251 microwave interstitial applicators can be inserted into 15.5 gauge (five French) radiation implant catheters.[92] The heating pattern is ellipsoidal and approximately 4.5 cm in length along the applicator shaft with heating to the applicator tip. Different heating patterns can be created using arrays of up to 24 applicators with eight independent microwave power channels. Both asynchronous and electronically-controlled synchronous phase modes are provided. The system monitors the temperatures of the target, which are typically 42–44°C, and the surrounding tissue, using sensors for invasive temperature measurement, and automatically limits the power to prevent the tissue from exceeding the maximum temperature specified by the user. Performing interstitial hyperthermia requires use of the BSD 500 built-in treatment planning

programme. Based on the size and shape of the tumour, the treatment plan can then be made by simulating the placement of the antennas in and around the tumour. The power and phase of each channel can then be set and opportunely optimised.

In EMEA the system requires room shielding because a frequency of 915 MHz is not ISM in such an area.

BSD 2000, BSD 2000 3D & BSD 2000 3D/MR systems (technical documentation and technical brochures downloaded from the company's website, we sought permission to use device images, but received no response from the manufacturer) [93-95].

The BSD 2000 3D/MR is a radiative hyperthermia system for the treatment of deep solid tumours.[96] The central operating frequencies of the radio-frequency power delivery system are variable and can be equal to 77 MHz, 90 MHz, 100 MHz and 110 MHz with a maximum radiated power of 1800 W. The system delivers energy to a patient by using a power source and an annular phased array of multiple antennas that surround the patient's body. The radiative technology is based on an array of eight dipole applicators grouped into four channels. These channels permit power to be focused on the target and move it in 2D (sigma 30/40/60) or by 12 channels to focus the power on the target and move it in 3D (BSD 2000 3D) to compensate for longitudinal patient positioning (sigma eye). The temperature that the tissues reach generated by the heating is in the range of 40°C–45°C. The temperature is measured for the entire duration of the treatment by means of probes placed in the patient. The system can be adapted to treat different-sized patients, from paediatric to adult patients. This is due to a circular array that is fixed but has various sizes that can be used in order to adapt the system to patients. Several circular arrays are available with diameters of 30 cm (sigma 30), 40 cm (sigma 40) and 60 cm (sigma 60) and there is also a square array of 37 x 53 cm^2 (sigma eye). The BSD 2000 system's water bolus is filled with circulating distilled water for both signal coupling and superficial cooling. It has a circular fixed size and is rigid.

The BSD 2000 3D has a thermometric system comprising eight channels and probes for real-time in-vivo dosimetry. No specific patient positioning systems are present. The hyperthermia system is equipped with a computerised control station and has a dedicated treatment planning system.

The BSD 2000 3D/MR can be coupled to a 1.5 Tesla MRI (Magnetic Resonance Imaging) system.[97, 98] In such cases, clear imaging visualization of the treated area is provided, permitting an accurate placement of the heat zone and an assurance of target temperature optimization. Heating and imaging can be conducted simultaneously for live temperature management. The operator can control the heat zone in 3D (along the X, Y and Z axes) by adjusting the frequency, phase and amplitude from multiple power sources. Energy can be focused electronically on the tumour region, thus providing dynamic control of the heating by the operator without having to reposition the patient.

The system requires room shielding because a frequency in the rage of 77–110 MHz is not ISM.

[A0020] – For which indications have different types of regional hyperthermia devices received marketing authorisation or CE marking?

Indications of hyperthermia systems for use in oncology are the adjuvant treatments of superficial and/or deep-seated primary and metastasized solid malignant tumours in combination regimen with chemotherapy and/or radiation therapy. The devices on the market are all CE marked but only a few are FDA authorized. These systems are also used outside the European and American markets and in such cases often have specific authorisations for the individual countries in which they are clinically applied.

[B0002] – What are the claimed benefits of regional hyperthermia for STS treatment in relation to the comparators?

Taking as reference what is reported in the company's documentation on hyperthermia systems for oncology, the claimed benefits of these treatments can be summarised as follows: i) improvement and extension of medical tumour control, ii) significantly higher success rates for treatment with chemotherapy and radiotherapy, iii) reduction of the tumour size enables removal by surgery, iv) destruction of tumour cells, especially in cases of previously treatment-resistant tumours, v) increased remission rates and improved quality of life, vi) long-term improvement of the course of the illness and vii) reduced risk of metastases.
The benefits of hyperthermia treatment have not yet been clearly proven,[12, 99] although some studies suggest possible benefits when it is used in combination with chemotherapy or radiotherapy, especially for advanced, recurrent or high-risk solid cancer.[28, 63, 78, 100-102]. It also shows that hyperthermia inhibits the repair of damaged cancer cells after chemotherapy or radiotherapy. These findings indicate that hyperthermia has potential for cancer therapy in conjunction with immunotherapy, chemotherapy, radiotherapy and surgery.
With greater clinical implications, a randomised phase III multicentre study on patients with high-risk STS has been published, including 341 patients treated before and after surgery with chemotherapy alone or with the addition of regional hyperthermia, both followed by radiotherapy.[29] The results of this study are presented and discussed in the EFF and SAF sections of this report.
The treatment's electrodes should not be placed close to plastic surgery implants (such as breast implants) and there are contraindications or patient groups for whom hyperthermia technology is not recommended.[87] These are: i) patients with pacemakers or built-in field sensitive devices (if not produced with the most recent standards of electromagnetic compatibility being taken into account). The applicability of hyperthermia also depends on the distance between the place of treatment and these built-in devices; ii) patients unable to communicate (babies, toddlers, patients in coma, or unconscious, patients in shock, etc.); iii) patients without temperature and pain perception in the treated area; iv) patients with epilepsy or those who are sensitive to electromagnetic fields; v) patients under immune suppression due to organ transplant; vi) patients who are unable to lie in the proper position for the treatment; vii) The applicator should not be applied over open wounds; viii) pregnant patients and ix) sedated or comatose patients.
Hyperthermia can be applied with special precautions in the following cases: i) to patients with acute systemic or localized infections or inflammatory processes; ii) to elderly patients who may experience a higher level of pain under the heavy applicator; iii) to areas with a high amount of fat.[87, 103] These areas must be closely monitored for surface burns and subcutaneous fibrosis; iv) thick hair in the treated area (hair, pubic hair, etc.) could hinder optimal application of the treatment and could cause surface burns; v) fluids in the treated volume may affect energy distribution (e.g. urine or ascites).

[B0003] – At what phase of development and implementation are regional hyperthermia devices in the treatment of STS and the comparators?

Hyperthermia is a type of medical modality for cancer treatment using the biological effect of artificially-induced heat. Even though it has been recognized as a therapeutic method for tumours, the intrinsic effects of increasing body temperature in cancer tissues are poorly understood. Hyperthermia is considered to inhibit the repair of damaged cancer cells after chemotherapy or radiotherapy and recent papers indicate that hyperthermia amplifies immune responses in the body against cancer while decreasing the immune suppression and immune escape of cancer.[104] Moreover, the anticancer effect of hyperthermia alone has not yet been adequately exploited.

It is therefore reasonable to hypothesize that the future of regional hyperthermia, including for STSs, will be oriented in two main directions: conducting studies using the existing devices will seek to better understand its clinical and biological effects, both in combined treatments and as a unique mode of therapy, and in the technological enhancement of the systems currently being marketed.[105] Studies are also looking at ways of reaching deeper organs and other sites that cannot be treated with hyperthermia at the present time. The introduction of more advanced pharmaceutical approaches and radiotherapeutic techniques, such as those using proton beams, also constitutes an additional field of research and development for hyperthermia.[106, 107] With reference to the devices, the improvement of the technology for better heat distribution at depth, as well as a broader introduction of hyperthermia treatment planning systems, constitute an important aspect. The treatment planning system comprises simulation software which, having defined the tissue dielectric map, calculated the distribution of the absorbed electromagnetic power and of the temperature in the patient's tissue, is able to guide the operator to evaluate and perform the best hyperthermia treatment plan in terms of tissue temperature (or Specific Absorption Rate) distribution, which is the optimal setting for a specific patient by varying the phase and amplitude parameters of each applicator.[10, 11] Increasingly more treatment planning systems from different companies (ALBA Hyperthermia system, Pyrexar Medical Int, etc.) are starting to appear on the market and are being used to improve hyperthermia treatments.
As the ESHO (www.esho.info, European Society for Hyperthermic Oncology) guidelines recommend basing hyperthermal dosimetry on temperature measurements only during the treatment (i.e. by means of thermometric probes positioned in the patient), the development of new and more effective methods for patient temperature monitoring certainly represents a field of future research.

[B0004] – Who administers regional hyperthermia and the comparators and in what context and level of care is it provided?

As described, hyperthermia is applied to STS in combination with other oncological treatments such as surgery, chemotherapy and radiotherapy. These oncological treatments are generally applied in secondary and tertiary healthcare, in specialised oncology units of hospitals and clinics. Since each hyperthermia session is generally carried out within a period of about one hour, the system is usually placed in the same institution in which oncology treatments are performed, or in centres that can be reached at the time indicated. However, hyperthermia treatment can be also performed as outpatient therapies.
The use of hyperthermia devices is straightforward because once the treatment has started, the system runs on its own. However, professionals who make decisions about starting or stopping the device and take care of the proper treatment process, must be properly authorized and trained. The trained professional can assist in setting the treatment positions, helping the patient onto the treatment bed and orienting the electrode to cover the tumourous area. The appropriate protocol must be selected, or the applied power and treatment duration must be set individually on the device. The treatment can be started after the self-check of the device. In general, all specialists who use the hyperthermia device (doctors, nurses, etc..) must be trained through specific courses by the company that has supplied the system.
In cases in which hyperthermia treatment requires special procedures, such as the invasive positioning of thermometric monitors, these activities must be performed by specialised professionals, each with their own specific skills (doctors, nurses). A situation becomes more complex when various professionals are involved, for example, when guidance is required (ultrasound, echo-Doppler, X-ray) and/or hyperthermia probes are to be inserted percutaneously or inside the brachytherapy catheters. Moreover, when a deep hyperthermia device is used in combination with an MRI system, MRI imaging experts must be involved for patient set-up check and for thermometry

verification procedures.[97] Also, an expert in planning calculation for hyperthermia treatment is required either during the pre-planning phase or on-line treatment delivery (temperature distribution) optimization.

[B0008] – What kind of special premises are required to use regional hyperthermia and the comparators?

A standard hyperthermia suite, in its broadest configuration, generally comprises a treatment room which is between 12 and 16m^2. Depending on the system being implemented, an operator room plus a small technical room may be required.[87, 103] For convenient patient handling, the treatment room is equipped with electromagnetic shielding and requires a floor area of around 24–35 m^2. The adjoining operator room requires a floor area of 12 to 16 m^2 and an observation window looking into the treatment room. A small technical room of 8 to 10 m^2 is required for installing the radio frequency power amplifier and any other computerized system. For certain systems with a minimal configuration, a standard room with a minimum 6–7m^2 of free space is sufficient. The floor must be able to support the equipment load. Specific requirements for building services, electricity, air conditioning and other relevant factors for each device can be found in the specific installation manual.
No Faraday cage (the same used for magnetic resonance imaging systems) is required for equipment operating in the field of frequency that falls in the ISM radio bands; the latter represents the portion of radio spectrum reserved internationally for the use of RF energy for industrial, scientific and medical purposes other than telecommunications. In such cases, users have no regulatory protection from ISM device operation. Thus, systems such as Alba On 4000 or EHY do not require room shielding in the EMEA region because they work at 434 MHz and 13.56 MHz, respectively, while other systems, such as the BSD-500, working at 915 MHz, the ALBA 4D and the BSD-2000, must be installed within a Faraday cage.

[B0009] – What equipment and supplies are needed to use regional hyperthermia and the comparators?

Regional hyperthermia is used in combination with chemotherapy and/or radiotherapy. To perform adequate treatment the operator needs some lying support and a thin cotton cloth to wipe away sweat. No other equipment is required.[87, 103] The hyperthermia suite should provide a nephrostomy/Foley bladder catheter to be used for the insertion of the temperature probe into the bladder, when required, or a catheter for the insertion of an interstitial temperature probe (not mandatory). Depending of the hyperthermia system, the device's electrodes must be changed after a certain number of treatment hours.

[A0021] – What is the reimbursement status of regional hyperthermia in the different EU countries?

• In **Germany** hyperthermia can be applied in the inpatient setting within the DRG flat rate but is not reimbursed in the outpatient setting (since 2005, it is included in the list of "overruled examinations or treatment methods").

• In **Switzerland** hyperthermia is reimbursed in cases with contraindications to chemotherapy. The reimbursement for deep hyperthermia will last until 31/12/2020 and will then be subject to reassessment.

• In **The Netherlands**, reimbursement is offered for superficial hyperthermia in combination with radiotherapy regardless of the indication, and for deep hyperthermia in combination with radiotherapy for recurrent rectal carcinoma and advanced stages of cervical carcinoma.

• In **Italy**, **Poland** and **Czech Republic**, superficial and deep hyperthermia are reimbursed regardless of the indications.

• In **Austria** hyperthermia is only offered in private settings.

• In **England** hyperthermia is not covered by national guidance and therefore possible decision making would be local.

• Limited information is available for **Scotland, Lithuania, Norway, Canary Islands (Spain),** where hyperthermia is either not offered or not reimbursed.
• In **all the other countries of the European Union not previously indicated**, when superficial and deep hyperthermia therapies are performed, they are not reimbursed.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What kind of sarcoma is in the scope of this assessment?
A0003	What are the known risk factors for high-risk STS?
A0004	What is the natural course of high-risk STS?
A0005	What are the symptoms and the burden of high-risk STS for the patient?
A0006	What are the consequences of high-risk STS for society?
A0024	How is high-risk STS currently diagnosed according to published guidelines and in practice?
A0025	How is high-risk STS currently managed according to published guidelines and in practice?
A0007	What is the target population of this assessment?
A0023	How many people belong to the target population?
A0011	To what extent are the technologies being utilized?

4.2 Results

Overview of the disease or health condition

[A0002] – What kind of sarcoma is in the scope of this assessment?

High-risk STS

This assessment is focused on high-risk STS, candidates for treatment with radio and/or chemotherapy, and for which the addition of hyperthermia is claimed to be beneficial. High-risk STS is a subgroup of sarcomas that originate from soft tissue and harbour an increased risk of local recurrence and distant metastases following treatment, resulting in high tumour-related mortality. There is no universally accepted definition of high-risk STS. However, some classifications are available. According to ESMO, high-risk sarcomas are defined as high-grade malignant tumours, situated deep to the subcutaneous fascia and large (size > 5cm).[3]

The ESMO guidelines recommend reporting the malignancy grade in all cases when this is feasible because of its prognostic and predictive meaning. The tumour grade describes how abnormal the cancer tissues and cells are compared to normal cells. The grade ranges from the lowest (i.e. Grade 1), which describes cells very similar to normal cells with a slow growth rate, to the highest (i.e. Grade 3 or higher), referring to very abnormal cancer cells with a high growth rate. The FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system is the most widely used for grading sarcoma and distinguishes three malignancy grades based on differentiation, necrosis and mitotic rate. [108-110]

A tool called Sarculator is also available and is used to predict the probability of overall survival and incidence of distant metastases for patients with STS, based on patient age, tumour histology, size and grade.[38]

High-risk STS include localised resectable, localised unresectable and advanced metastatic tumours. The object of this assessment is high-risk localised resectable STS eligible for neoadjuvant and/or adjuvant chemo-radiotherapy, localised unresectable and inoperable advanced metastatic STS treated with chemo-/radiotherapy only. Advanced STS with isolated pulmonary metastases, which are treated with surgery only, are not eligible for this assessment since chemo-/radiotherapy are not used due to their limited beneficial effect.[3] In this assessment we included high-risk STS occurring in different locations, i.e. extremity, trunk, head and neck, and retroperitoneal.

Description of sarcoma and subtypes

Sarcomas are a rare and heterogeneous group of malignant tumours of mesenchymal origin; mesenchymal stem cells are those that develop into myocyte, adipocyte, osteoblast, chondrocyte, neuron, connective tissue, blood vessels and lymphatic tissue. Sarcomas comprise less than 1% of all adult malignancies and 12% of paediatric cancers.[111, 112]

The majority of new cases originate from soft tissue (approx. 80%) and the rest originate from bone.[64, 112, 113]

STS include up to 100 different histological subtypes, classified by the World Health Organisation according to the presumptive tissue of origin, which corresponds to the normal tissues the tumour most closely resembles (i.e. liposarcoma, leiomyosarcoma, rhabdomyosarcoma, fibrosarcoma and angiosarcoma). Moreover, when histogenesis is uncertain, the designation reflects the architectural pattern (e.g. alveolar sarcoma of soft parts, epithelioid sarcoma, clear cell sarcoma).[114] The most common subtypes are GIST, which are not included in this assessment due to their different treatment strategies compared to other STSs.[115]

Different subtypes have a wide range of biological behaviours, from clinical presentation to prognosis.[64, 114] For example, liposarcomas, arising from precursors of adipocytes (fat cells), are most commonly found in the retroperitoneum and extremities and have very different morphological subgroups, spanning from well-differentiated liposarcoma with no metastatic potential to the high-risk round cell or pleomorphic types, which tend to be higher grade and are associated with a high rate of distant metastases.[114, 116, 117] Other common STSs are leiomyosarcomas, characterized by smooth muscle differentiation, which can occur throughout the body, in any location in which there is a vein, including the retroperitoneum and the uterus. There are also cutaneous leiomyosarcomas, which typically have a more indolent course and are less likely to metastasize, unlike superficial and deep tumours.[118, 119] Angiosarcomas are also less common and occur in many sites of the body, especially in subcutaneous tissue, typically of the head, neck or breast treated for cancer, as it is commonly caused by therapeutic radiation, or following treatment for Hodgkin's lymphoma, with a median time of development of 8 to 10 years.[120, 121] Other subtypes of STS are synovial sarcoma, commonly detected in the extremities of young adults, malignant peripheral nerve sheath tumours that originate in the peripheral nerves, mainly in patients with neurofibromatosis type I, and solitary fibrous tumours, slow-growing tumours that occur most commonly in the pleura, pelvis or dura, where they can reach a very large size before detection.[114, 116, 122]

Undifferentiated/unclassified STS, formerly generically termed malignant fibrous histiocytoma (MFH) are now identified as pleomorphic (undifferentiated pleomorphic sarcoma), round cell and spindle cell variants, which simply describe histological morphology. [123] One formerly termed myxoid malignant fibrous histiocytoma is now classified as myxofibrosarcoma and may be associated with a greater risk of local recurrence.[64, 124, 125]

ICD Classification:

Eligible cases for this assessment are coded as follows: malignant neoplasm of peripheral nerves and autonomic nervous system, or connective, subcutaneous and other soft tissue (ICD-O-3 topography C47, C48 and C49); ICD-O-3 morphology malignant behaviour code in the ranges: 880* (soft tissue tumours and sarcoma NOS), 881*-883* (fibromatous neoplasm), 884* (myxomatous neoplasm), 885*–888* (lipomatous neoplasm), 889*-892* (myomatous neoplasm), 893*–899* (complex mixed and stromal neoplasm) , excluding GIST 8936/*, 904 (synovial like neoplasm), 912*–913* (blood vessel tumours), 917* (lymphatic vessel tumours).[19, 20]

[A0003] – What are the known risk factors for high-risk STS?

Most STSs have no clearly defined aetiology. Despite this, a number of associated or risk factors have been identified, including genetics, viral and environmental factors.[111, 113, 126, 127]

Genetic factors
Among genetic factors there are inherited syndromes such as Li-Fraumeni syndrome, familial adenomatous polyposis, retinoblastoma and neurofibromatosis.[111, 113] Acquired gene alterations in specific genes vary across histological subtypes of STS, and specific nonrandom chromosomal translocations, which now serve as definitive diagnostic criteria for the tumours in which they occur.[128-131]

Environmental and other factors – Radiation therapy
Radiation therapy is recognized as a cause of sarcomas of soft tissue and bone, as the incidence correlates with the radiation therapy dose and with the post-radiation observation period. The risk of a radiation-induced sarcoma is high in childhood cancer survivors and highest in those who receive both radiation therapy and chemotherapy (particularly anthracyclines and alkylating agents), as well as in those treated for a primary sarcoma.[111, 113, 127, 132]

Industrial chemicals
Among occupational exposures, few associations can be considered as established and causal, mainly due to the small number of patients and the difficulty of isolating a single exposure.[113, 126, 127, 133] There is a clear association between vinyl chloride exposure and hepatic angiosarcoma [134, 135] and a probable association between phenoxy herbicides and STS.[136, 137] The latter risk may be greater with exposure to phenoxy herbicides contaminated with dioxin, the role of which, *per se*, remains controversial.[138-140]

Chronic oedema, chronic irritation and trauma
The risk of soft-tissue-sarcoma is also increased in chronic conditions such as massive and quite protracted oedema (primarily lymphangiosarcomas), classically seen in the postmastectomy lymphoedematous arm (i.e. Stewart-Treves syndrome) or in chronic lymphedema due to filarial infection.[141, 142] An association with the incidence of STSs, including desmoid tumours, has been found with trauma or chronic irritation due to foreign bodies. However, this association is not clear, as the chance finding of a previously undetected mass might occur when investigating the consequences of a traumatic incident.[143] Since injury has been shown to promote sarcoma development in animal models, additional studies are needed to determine the role of injury in sarcomagenesis.[144, 145]

Viral infections
The following viral infections are associated with the development of STSs: Human Immunodeficiency Virus (HIV), Human Herpes Virus 8 (HHV-8) and Epstein-Barr Virus (EBV).
HIV and HHV-8 have been implicated in the pathogenesis of Kaposi sarcoma, while Epstein-Barr Virus (EBV) has been found associated with smooth muscle tumours in immunocompromised patients (i.e. with HIV/AIDS or following solid organ transplant).[129, 146-149]

[A0004] – What is the natural course of high-risk STS?

As for morphological characteristics, the natural history of STSs is also characterized by a wide range of different behaviours, in pattern of growth, spread and recurrence.

Pattern of growth
The rate of growth depends on the aggressiveness of STSs, ranging from high growth rates to slow-growing tumours such as solitary fibrous tumours and well-differentiated liposarcoma.[114, 129]

In general, STSs grow along tissue planes compressing the surrounding normal tissue and only rarely traverse or violate major fascial planes or bone. STSs tend to grow centrifugally pushing the surrounding tissue. During this process, a pseudocapsule of compressed tissue and inflammation develops around the tumour, which often contains micro-satellites of tumour tissue. Because tumour cells can be found extending beyond the pseudocapsule, dissection along the pseudocapsule plane should be avoided or should be supplemented with radiation treatment to decrease local recurrences. Removal of soft tissue alone in the radial plane is not sufficient to achieve a wide margin.[129]

Pattern of spread
In STSs, the most common pattern of spread is haematogenous, while the spread to regional nodes is infrequent.
Generally, the presence of distant metastatic disease at the time of initial diagnosis is uncommon (almost 10%), predominantly located to the lung, and is more frequent in large, deep, high-grade sarcomas, and in specific histologies (i.e. soft tissue Ewing sarcoma, malignant peripheral nerve sheath tumour (MPNST), and extraskeletal chondrosarcoma).[150]
Similarly, the spread to regional nodes that occurs in almost 3% of STSs has a different frequency depending on histology, with the greatest risk for rhabdomyosarcoma, synovial sarcoma, epithelioid sarcoma, clear cell sarcoma and the vascular sarcomas.[151]
It must be also said that lymph nodal metastases carry a poor prognosis, although somewhat less than overt bloodborne metastases.[64, 151-153]

Pattern of recurrence
After treatment of a STS, recurrence can occur as a local or metastatic disease, with an incidence rate depending on anatomic location, extent of resection, use of perioperative radiation therapy and histology.[154, 155] The average incidence of recurrence after successful treatment of a primary STS is approximately 25% and much higher (40 to 50%) in tumours that are >5 cm in size, deep to the fascia, and intermediate or high grade.[156, 157] As previously reported, metastatic disease to the lungs occurs in almost 80% of cases [150, 154], while rare sites of metastatic spread include the skin, soft tissues, bone, liver and brain.[154, 158, 159]
Some exceptions to the typical pattern of metastatic disease involve round cell/myxoid liposarcomas, (with common extrapulmonary metastases to the retroperitoneum, abdomen, bone, (particularly the spine), and paraspinal soft tissue.[160, 161] Moreover, retroperitoneal leiomyosarcomas commonly metastasize to the liver as well as the lung, while retroperitoneal liposarcoma is characterized by locoregional recurrence rather than by distant metastases.[162, 163]
Notably, for head and neck sarcomas, the natural history parallels that of non-head and neck sarcomas with the same characteristics, but with a higher rate of local recurrence after treatment.[164]

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of high-risk STS for the patient?

Clinical presentation

STSs can originate in all anatomic body sites, but mainly in the extremities. A review of 4,550 adults with STS described the following anatomic distribution: 46% of cases presenting in thigh, buttock and groin, followed by 18% in torso, 13% in both retroperitoneum and arms, and 8% in head and neck.[64, 165]

The clinical presentation of STSs is strictly related to their natural history and the site of origin, commonly presenting as a gradually enlarging, painless mass, that can become quite large before causing symptoms, especially in the thigh and retroperitoneum.
The most common symptoms are pain, paraesthesia or oedema in an extremity, generally associated with compression by the mass. Constitutional symptoms, such as fever and weight loss, are rare at diagnosis.
Retroperitoneal sarcomas typically come to medical attention as an incidentally discovered abdominal mass in asymptomatic or minimally symptomatic patients since mass can grow substantially before compressing the surrounding structures.[112]
Uterine sarcoma has a typical presentation, characterised by the presence of abnormal uterine bleeding, pelvic pain and pressure, and the presence of a uterine mass.[166]

Head and neck sarcomas are diagnosed in patients with a palpable mass (especially in the neck), skin changes (especially on the scalp or face), or subsite-specific symptoms (e.g. hoarseness with laryngeal primaries, dysphagia with oropharyngeal tumours, epistaxis, nasal obstruction, or cranial nerve deficits with skull base tumours).[108, 124, 166]

Finally, some histological types of STS tend to show a predilection for certain anatomic sites, although the anatomic distribution of histological subtypes is not only related to the abundance of the tissue type.[64, 167, 168]

Quality of life

Like any oncological disease, a diagnosis of STS can also impact the physical and psychological well-being of patients.[169-171]
Recent systematic reviews highlight the lack of studies assessing STS-specific patient-reported outcomes, leading to a lack of evidence on the specific needs of this population.[169, 170]
Despite this, many studies have assessed items related to global health status, functioning scales, and symptom scores, comparing patients with STS with the general population and patients at different stages of treatment. As expected, the physical and psychological conditions are definitely worse in patients with STS, but the treatment impacts the global health status and symptoms scores more than on functioning scales.[170]

Recent analysis of data collected from the National Cancer Patient Experience Surveys, including 900 patients of different age, reported the symptoms and concerns of people diagnosed with STS (75%) and bone sarcoma (25%).[171]
The most commonly reported symptoms were daytime fatigue and pain, especially in younger patients, followed by many others symptoms with differences by age groups (Figure 7).
Regarding psychological well-being, younger patients were also more likely to report post-treatment concerns than older patients and were less satisfied with the information and emotional support provided. The list of post-treatment concerns and differences by age groups are reported in

Figure 8, clearly suggesting the need of an age-specific approach to STS patients in order to improve the overall experience.[171]
This study also focused on differences in the sarcoma patient's diagnostic pathway, reporting a delay in diagnosis in 27% of patients, with younger patients being more likely than older patients to be misdiagnosed and treated for other conditions, or having their symptoms underestimated.[171] The high complexity and challenges of the diagnostic pathway and its impact on quality of life have been highlighted by a further study conducted in the UK and based on the National Cancer Data Repository, including patient-level data on 7,716 soft tissue and 1,240 bone sarcoma diagnosed between 2006 and 2008.[172] The authors showed that only 12.5% of STSs are diagnosed through the "two-week wait" (TWW, urgent general practitioner referral, cancer suspected) system under which patients with suspected cancer must be seen within two weeks. The most frequent route to diagnosis of STS starts from a non-TWW general practitioner (GP) referral (33.6%), followed by 17.8% presenting in an accident and emergency setting, 15.8% from outpatients referral as opposed to GPs and 7.0% after elective admission for other causes.[172]

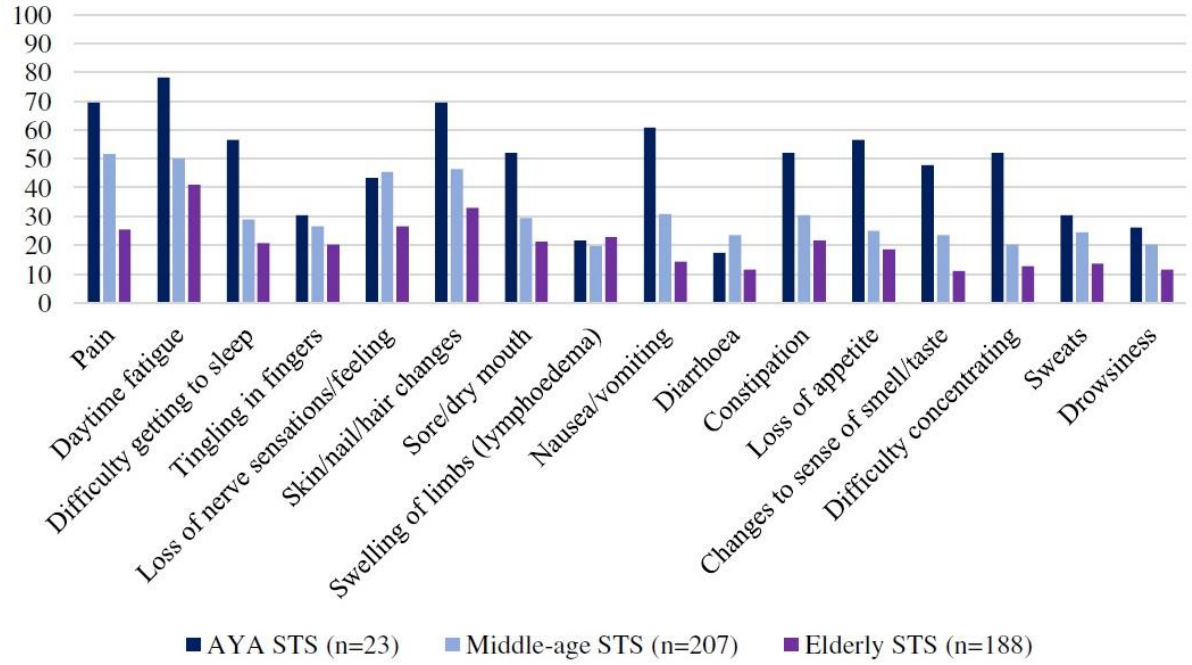


Figure 7 Percentage of STS patients with symptoms or side-effects according to the different age groups. Heading – STS (AYA = Adolescents and Young Adults STS (n = 23), Middle-Age STS (n = 207), Elderly (n = 188). Reproduced from Younger et al. 2018.[171]

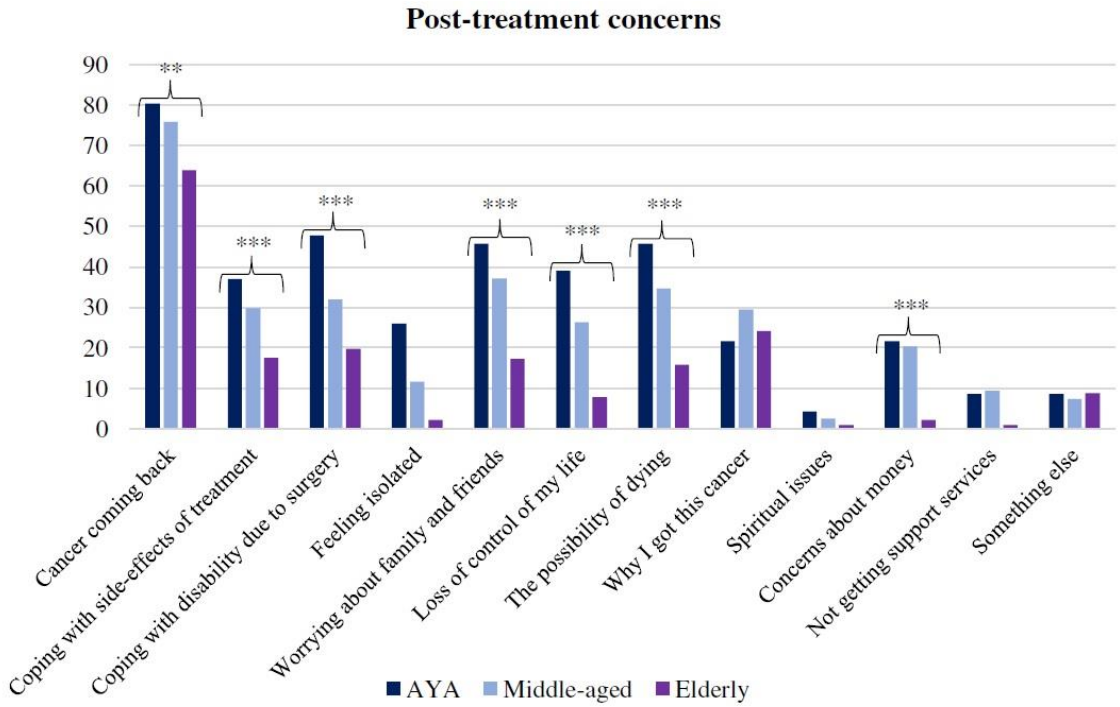


Figure 8 Percentage of sarcoma patients with post-treatment concerns according to age groups. (AYA = Adolescents and Young Adults; ** P<0.01; ***p<0.001). Reproduced from Younger et al. 2018 [171].

A recent systematic review of studies assessing quality of life reports the relevant financial and social impact of an STS diagnosis, measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: Core 30.[170, 173]
Compared to the general population, patients with STS reported greater financial difficulties resulting from their physical condition or medical treatment. The review authors also highlight the importance of considering, early in the treatment process, the supportive network (i.e. family/caregiver assistance and living situation) of patients with STS.[170]
Since STSs are relatively rare cancers and should be treated in specialized centres, they lead to a higher resource demand for patients living in more remote areas. Thus, the financial and social impact raises the issue of inequity in the management of this disease.[170, 174]

[A0006] – What are the consequences of high-risk STS for society?

As a rare disease, STS has a much higher impact on the individual patient than on society. Despite this, two main issues related to these diseases should be approached from a societal perspective. The first is related to equity and the second to healthcare resource use and costs.

The evidence suggests that socioeconomic factors have an impact on quality of healthcare and a prognosis of STS. Brennan and colleagues highlighted the highest hazard ratio in the most deprived quintile of patients with synovial sarcoma from the English National Cancer Registry.[174] Moreover, in a previous US study based on the cancer registry data of the Surveillance, Epidemiology, and End Results Program, a lower disease-specific survival was observed in African-Americans patients compared to other patients, as well as in those living in rural compared to urban areas.[175] This factor calls for an effort to reduce the disparities in access to healthcare services and also in improving early diagnosis of STS in more deprived subgroups of the population.[172, 174] Indeed, from the perspective of introducing a new technology in cancer treatment, its impact on equity should be taken into account.

Regarding the healthcare resource use of patients with STS, despite the relatively low incidence of STS, the estimated impact of lifetime costs of a patient with STS is relevant and also very different across countries, mainly due to differences in the respective healthcare systems.[176-178]

The SABINE multi-centre retrospective chart review study of metastatic patients with STS analysed healthcare resource utilisation of patients with favourable response to chemotherapy in nine high-income countries: Canada, France, Germany, Italy, the Netherlands, Spain, Sweden, UK and the USA. The expected per-patient lifetime medical cost was EUR 65,616 (95% CI: EUR 51,454–85,003); comprising IV chemotherapy (31.7%), inpatient care (24.8%), concomitant medication (11.0%), oral chemotherapy (8.9%), outpatient visits (8.8%), radiotherapy (6.3%), hospice (4.0%), imaging (3.7%) and laboratory (0.7%). A wide range of estimated per-patient lifetime medical costs have been found, from EUR 25,547 in The Netherlands to EUR 228,661 in the USA.[177]

Another international study estimated healthcare resource utilization and cost for patients with advanced STS in the UK, Spain, Germany and France, based on data provided by 130 physicians on 807 patients. In this study, the total mean per-patient healthcare cost was lower than in the previous study, ranging from EUR 20,468 in Germany to EUR 26,814 in Spain. This was mainly due to the selection criteria of the different patients. This study showed that advanced STS-related systemic treatment costs were primarily driven by drug acquisition and administration costs.[178]

Current clinical management of the disease or health condition

[A0024] – How is high-risk STS currently diagnosed according to published guidelines and in practice?

Sarcoma patients usually present a new or growing lump. The lump may be painless until it creates pressure on nerves or organs. If a tumour is located in the abdomen, it may obstruct and cause bleeding of the bowels or stomach. This can present as abdominal pain.

The initial evaluation of a patient with a suspected STS begins with a history of when the mass was first noticed, how quickly it has been growing, and whether there are symptoms to suggest distal neurovascular compromise.

Magnetic resonance imaging (MRI) is the main technique for detecting masses in the extremities, pelvis and trunk that could result in STS. Computed tomography (CT) plays a role in calcified lesions and is the main technique for detecting retroperitoneal and abdominal sarcomas. A chest spiral CT scan is mandatory for staging. The decision to use a bone scan, whole body MRI and PET is made in light of considerations regarding suspicion of advanced disease.

Following appropriate imaging assessment, the standard approach to diagnosing sarcoma is to perform multiple core needle biopsies. Excisional biopsy is the most practical option for superficial lesions <3cm and open biopsy may be an option in selected cases, even if generally discouraged – to be performed after discussion with experts at a referral centre. Tumour size and depth have a prognostic value, along with malignancy grading. The pathology report, after definitive surgery, should mention whether the tumour was intact and must include an appropriate description of margins (made in collaboration with the surgeon), especially the distance in millimetres between tumour edge and the closed inked margins. Due to the specific requirements, pathological examination should be conducted by a sarcoma pathologist.

Histological grade — Histological grade is an independent indicator of the degree of malignancy and the probability of distant metastases.[114, 123, 179, 180] However, histological grade is a poor predictor of local recurrence, which is mainly a function of surgical margins.

Several grading systems have been developed over time to increase the prognostic value of histological assessment, some of which use a three-tier system (i.e. grade 1 [well differentiated, low grade], 2 [moderately differentiated] or 3 [poorly differentiated, high grade]). The three-tiered system is incorporated into the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) staging system for STSs and is the preferred system. [114, 181] The FNCLCC grading system is preferred by the College of American Pathologists (CAP) and is based on differentiation, mitotic activity and necrosis [Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with STS. [108] Grading is not applicable to all STSs. It is of little prognostic value for MPNST and is not recommended for angiosarcoma, alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma and epithelioid sarcoma. [181]

Tumour size – The risk of developing a local recurrence and distant metastases increases substantially with increasing tumour size. [182-184]

In a retrospective study from the Massachusetts General Hospital (MGH), the frequency of distant metastases in high-grade tumours as a function of tumour size was as follows [184]:

- Tumours ≤2.5 cm – 6%
- Tumours 2.6 to 4.9 cm – 23%
- Tumours 5 to 10 cm – 38%
- Tumours 10.1 to 15 cm – 49%

- Tumours 15.1 to 20 cm – 58%
- Tumours >20 cm – 83%

Another study divided 316 patients with STSs into four subgroups on the basis of tumour size (less than 5 cm, 5 cm to less than 10 cm, 10 cm to less than 15 cm, and greater than 15 cm). Each subgroup was found to have a different prognosis, with five-year survival rates of 84, 70, 50, and 33%, respectively.[183]

Prognostic tools — Estimating prognosis in patients with STS is important for patient counselling and for therapeutic decision-making. In addition to stage, grade and tumour size, factors associated with survival include anatomic site, age and histological subtype. Prognostic nomograms incorporating such variables are useful tools in patient management.

The most widely-used nomogram (which applies to all anatomic sites) is the postoperative nomogram for 12-year sarcoma-specific death from MSKCC.[185] This nomogram is also available online [186] and has been validated with an external cohort of patients who were treated at the University of California-Los Angeles (UCLA).[187] The histological grade in the MSKCC nomogram was defined as high or low according to previously published criteria.[188] A subsequent adapted nomogram has been published incorporating the FNCLCC three-grade classification.[187]

A separate prognostic nomogram is available for retroperitoneal sarcoma that also includes the FNCLCC grade and the extent of resection.[186]

The Scandinavian Sarcoma Group has meticulously developed a risk system in high-grade STS in order to select patients for adjuvant chemotherapy. The system takes into account the following risk factors for disease recurrence: tumour size, vascular invasion, tumour necrosis and infiltrative growth pattern.[189-193]

As previously mentioned, the Sarculator tool is also available to predict the probability of overall survival and incidence of distant metastases for patients with STS, based on patient age, tumour histology, size and grade.[38]

[A0025] – How is high-risk STS currently managed according to published guidelines and in practice?

Because of its rarity and the frequent need for multimodality treatment, guidelines recommend that evaluation and management of STS should ideally be carried out at a centre with expertise in the treatment of sarcomas, including surgical oncology, orthopaedic surgery, plastic surgery, adult or paediatric medical oncology, radiation oncology and a high volume of treated patients. The multidisciplinary team approach to care of STS optimizes treatment planning, minimizes duplication of diagnostic studies and reduces the time to implementation of the definitive therapeutic protocol. All patients with an unexplained deep mass of soft tissue or a superficial lesion >5cm should be immediately referred to a multidisciplinary expertise centre.

- **Management of high risk (grade 2/3 and size >5cm) local/locoregional resectable STS:**

Before surgery (which is the standard treatment), both the ESMO and NCCN guidelines allow for a possible role of neoadjuvant radiotherapy and/or chemotherapy in the case of deep lesions. However, no definitive evidence is available regarding their benefit-risk ratio and specific approaches are decided on a case-by case basis by a multidisciplinary team, which takes into account histological and clinical heterogeneity. In particular, neoadjuvant therapy is considered in cases of large or recurrent high-grade tumours, most often using radiotherapy with or without chemotherapy. [22, 83]
More specifically, the ESMO guidelines specify that if wound complications are anticipated to be manageable, a total dose of 50 Gy in 1.8–2 Gy fractions of neoadjuvant radiation therapy (RT) may be considered, possibly in combination with chemotherapy (ChT) for tumour control and better late functional and cosmetic results.[3, 22, 194]

As for trial results, in a recent international multicentre RCT, standard neoadjuvant chemotherapy has proven to be more effective than histotype-specific chemotherapy on disease-free survival [195]. Instead, preliminary data from the STRASS trial showed no benefit of neoadjuvant radiotherapy for retroperitoneal STS. [196] Limited data are available to support one approach over the other.
One Canadian RCT including 190 patients with primary or recurrent extremity STS showed a similar efficacy of preoperative (50 Gy) or postoperative (16 to 20 Gy boost) radiotherapy, with a higher rate of generally reversible acute wound healing complications in preoperatively treated patients counterbalanced by a lower rate of irreversible late complications.[197]
As for chemoradiotherapy, there is lack of RCTs to compare this strategy vs. radiotherapy alone, as well as RCTs comparing different combinations of chemo- and radiotherapy. There is no consensus on an optimal approach to chemoradiotherapy, with some centres using single-agent doxorubicin, others preferring sequential RT and an anthracycline plus ifosfamide-based chemotherapy regimen, or RT combined with alternative chemotherapy agents (such as gemcitabine).[22]

Surgical procedures generally consist of performing a wide excision with clear margins. It is strongly recommended to remove the tumour with a rim of normal tissue around it. [3] The minimal margin of clear tissue depends on several factors, such as histological morphology, preoperative therapies and the presence of anatomical barriers. Marginal excision is only acceptable in selected case, in particular in the case of extracompartmental atypical liposarcoma.

Guidelines recommend that a typical wide excision with clear margins (R0) is followed by adjuvant radiotherapy and/or chemotherapy, if not given preoperatively. [3, 36] Re-operation in reference centres must be considered in the case of a microscopic tumour at the margins (R1), if adequate margins can be achieved without major morbidities. In the case of a macroscopic tumour at the margins (R2), re-operation in reference centres is mandatory.

In the case of R1 margins, adjuvant radiotherapy is recommended if R0 resection is not feasible. According to the ESMO guidelines, radiotherapy should be administered with the best technique available, to a total dose of 50 Gy in 1.8–2 Gy fractions, possibly with a boost up to a total of 66 Gy, depending on presentation and resection margins.[3] Mutilating surgery may be utilized in some cases.
As for adjuvant chemotherapy, a meta-analysis of 18 RCTs on individual patient data published in 2008, including 1,953 patients, showed an odds ratio for local recurrence of 0.73 (95% CI 0.56 to 0.94) in favour of chemotherapy.[198] Five of the trials used doxorubicin plus ifosfamide, while the other trials used doxorubicin alone or in combination with other agents. The absolute risk reduction for doxorubicin in combination with ifosfamide was 11% (30% versus 41% risk of death). Benefit could not be shown for doxorubicin alone, implying the importance of ifosfamide in the adjuvant treatment of sarcomas. However, this meta-analysis has wide margins of uncertainty as it did not include the two largest trials, both conducted in Europe and both testing the value of an anthracycline and ifosfamide-containing regimen: a pooled analysis of both trials indicated no benefit from this approach on overall survival.[199] Additional up-to-date evidence on the positive effect on metastases-free survival of adjuvant therapy with doxorubicin and ifosfamide comes from a prospective non-randomised trial on 150 patients.[193]

- **Management of local/locoregional unresectable STS:**

The ESMO guidelines recommend chemotherapy and/or radiotherapy as first lines of treatment to reduce tumour volume and increase the possibility of resecting it. [3] If RO or R1 are feasible, then surgery is recommended with subsequent radiotherapy. If R0/R1 surgery remains unfeasible, advanced disease approaches should be followed. Hyperthermic limb perfusion with TNF-alpha plus melphalan could also be considered.[3]

- **Management of advanced/metastatic resectable STS:**

If non-pulmonary distant metastases are diagnosed during staging, surgery is not recommended and recommendations for unresectable metastatic sarcomas should be followed. If unilateral metachronous lung metastases (>=1-year disease free survival) are diagnosed, the ESMO guidelines recommend resecting the metastases, if complete excision of all lesions is feasible. Abdominal CT scans and bone scans or FDG-PET are considered mandatory for confirming that lung metastasis is isolated and resectable. Anthracyclin-based chemotherapy may be added to surgery, although there is a lack of evidence that it improves outcomes. Chemotherapy is preferably given before surgery in order to assess the tumour response. In cases of pulmonary synchronous metastase, chemotherapy followed by surgery of completely resectable lung metastasis is recommended.

- **Management of advanced/metastatic unresectable STS:**

Anthtracycline-based chemotherapy (doxorubicin) is the recommended treatment according to the ESMO guidelines. Multiagent chemotherapy adding isofosfamide can be considered in subtypes that are sensitive to it. Taxanes, dacarbazine and imatinib may be alternative options for combined chemotherapy, depending on the histological subtype. There is no evidence that multiagent chemotherapy is superior to single agent with doxorubicin alone. If there is no partial response or stable disease, another histology-driven therapy is attempted. If there is a partial response or stable disease, chemotherapy should continue until progressive disease or unacceptable toxicity.[3, 200]

Follow-up

There are few data and no strong recommendations to indicate the optimal follow-up guidelines. The grade affects the probability and aggressiveness of relapses. High-risk sarcomas generally relapse within 2–3 years with distant metastases. There is no evidence that a CT scan or MRI are more beneficial or cost/effective in detecting recurrences earlier compared to a chest X-ray. While further studies are needed, a practical approach is as follows: moderate/high grade sarcomas monitored every 3–4 months in the first 2–3 years, then twice a year up to the fifth year and once a year thereafter.

Rationale for an HTA on hyperthermia in STS treatments

Several factors can influence the effectiveness and safety of STS treatments, considering the wide variety of clinical scenarios arising from the involvement of different anatomic sites, histologies, grade and tumour size. However, the expertise of the clinical centre and a multidisciplinary team approach can positively influence clinical outcomes through the multimodality of treatments and individualized therapeutic protocols. Indeed, the major therapeutic goals for patients with STS are survival, avoidance of local recurrence, maximizing function and minimizing morbidity. [22, 23]

As previously reported, surgery is the first choice for all localised operable tumours, with the objective of obtaining a margin-negative resection. Unfortunately, in real practice this objective is not always achievable, particularly for high-risk STS. In this group of STS, multimodality treatments are generally recommended, yet there is a lack of strong evidence. Radiation therapy and chemotherapy can be considered in therapeutic protocols, either as neoadjuvant or adjuvant therapy in resectable tumours, as well as systemic in inoperable metastatic STS.[3, 194]

In this context, regional hyperthermia, combined with chemotherapy and radiotherapy, could have an emerging role as a limb-sparing technique for patients with high-grade STS, if toxicity is low and if the response to chemotherapy and radiotherapy improves. These characteristics could make hyperthermia an option to consider for its potential for improving patient outcomes in the treatment of high-risk STS. Guidelines are generally elusive about its role, although isolated hyperthermic limb perfusion with tumour necrosis factor alpha (TNF-alpha) plus melphalan is one of the recommended options of the ESMO guidelines.[3] Recently updated evidence shows its potentially positive impact on objective response rate, disease-free survival and overall survival, and as an option for limb-preserving surgery, although the quality of available evidence is limited.[83] Another option is systemic chemotherapy (doxorubicin, ifosfamide, and etoposide) combined with regional hyperthermia: one RCT suggests that this strategy may prolong survival in patients with localised deep high-risk STS vs. chemotherapy alone (HR 0.73; 95% CI, 0.54-0.98).[28] These elements provide a rationale for an extensive assessment of the effectiveness and safety of the use of hyperthermia in high-risk STS therapeutic protocols, combined with other treatment techniques.[28, 29, 57, 83, 201, 202]

Target population

[A0007] – What is the target population of this assessment?

Adults (>18yrs) who have a high-risk STS, excluding adolescents or children, given that STS is a very rare disease for this age group and treatment in these age groups follows specific paediatric protocols.

Within this assessment we have included both non-metastatic localized and metastatic sarcomas in which the cancer has spread from the main tumours to other areas in which chemo-/radiotherapy is a treatment option.

[A0023] – How many people belong to the target population?

Adult soft tissue and visceral sarcomas (excluding GIST) are rare tumours, accounting for less than 1% of all new incident cancer cases, with an estimated incidence averaging 4–5/100,000/year in Europe. There is a slight male preponderance of 1.4:1 [17] The median incidence age is 59 with a bimodal distribution that peaks in the fifth and eighth decades. [18]

STSs include up to 100 different histological subtypes and the most frequent, liposarcomas and leiomyosarcomas (LMSs), have an incidence < 1/100,000 per year, followed by undifferentiated pleomorphic sarcoma. Thus, the majority of sarcoma histotypes have an incidence rate of <2/1,000,000 per year. [3, 20, 123, 180]

The most important prognostic factors in STS are histological grade, tumour size, anatomical location and pathological stage at the time of diagnosis. In a US series using the seventh edition TNM stage groupings, disease-free survival for stage I, II, and III disease at five years was 86, 72, and 52%, respectively, with a corresponding overall survival of 90%, 81%, and 56%, respectively. [179, 203]

[A0011] – To what extent are the technologies being utilized?

About 10% of diagnosed STS are metastatic at diagnosis [150] while 40–50% will develop metastatic disease, thus limiting treatment options, especially surgery. [204] Chemotherapy (doxorubicin alone or in combination) is most commonly used for advanced STS, but the intent is generally palliative rather than curative, with a low response rate (10–25%). [205]

A retrospective observational study in four European countries (n=807) showed that 63.7% of diagnosed STSs had grade 3 histology, 73.4% with tumour size >5cm and 81.2% deep invasion. Among metastatic patients, the most common site of metastatic localization is the lung (70%). [206] All patients received at least one line of adjuvant chemotherapy. Overall, 56% received only first-line therapy, 32.5% two lines of chemotherapy and 11% at least three lines of chemotherapy. The most commonly used therapy is doxorubicin (68.4%), followed by ifosfamide (40.2%), gemcitabine (24.7%) and docetaxel (20%). [206] The most common first line systemic treatment in Europe is doxorubicin alone (41%), followed by doxorubicin plus ifosfamide (19%), docetaxel plus gemcitabine (8.7%) and paclitaxel (4%). [206] Multiagent chemotherapy has not shown a superior response compared to doxorubicin as a single agent. [207]

Data from the Hospital Inpatient National Statistics (HCUPnet) in the USA show that rate of Hyperthermia procedures for treatment of cancer (ICD-9-CM Codes: 99.85) have increased from 0.20*100000 in 2010 in to 0.44*100000 in 2015. [208] No studies in Europe have quantified the use of hyperthermia, which is primarily used in a few specialized clinics where it is present and utilized for research purposes, or in selected cases.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect on mortality of non-invasive regional hyperthermia in addition to chemo-and or radiotherapy?
D0005	How does non-invasive regional hyperthermia affect the symptoms and findings (severity, frequency) of STS?
D0006	How does non-invasive regional hyperthermia affect the progression (or recurrence) of STS?
D0011	What is the effect of non-invasive regional hyperthermia on patients' bodily functions?
D0012	What is the effect of non-invasive regional hyperthermia on generic health-related quality of life?
D0013	What is the effect of non-invasive regional hyperthermia on disease-specific quality of life?
D0017	Were patients satisfied with non-invasive regional hyperthermia?

5.2 Results

Included studies

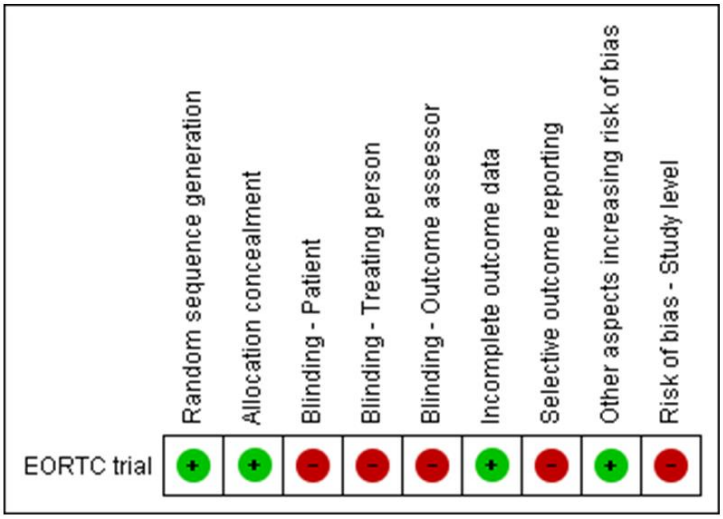
For this domain we have used evidence from the EORTC RCT. We refer hereafter to the EORTC trial (NCT 00003052, Issels 2010, Issels 2018) EORTC 2010 or EORTC 2018 to report results from both trials, the 2010 or 2018 publications, respectively. Median follow-up times for the outcomes reported in EORTC 2010 were three years in the intervention group that received hyperthermia and 2.6 years in the control group. The median follow-up duration in EORTC 2018 was 11.3 years (interquartile range 9.2–14.7 years).[28, 29] . We did not report intermediate follow-up data from the 2010 publication if final data were available from the 2018 publication (i.e. HR and median duration time for progression-free survival and disease-free survival).

The EORTC RCT enrolled 341 patients from nine centres in four countries (six centres in Germany, one in Norway, one in Austria, one in the USA). The patients were randomised equally to an intervention group that received four cycles of chemotherapy + regional hyperthermia neoadjuvantly, followed by best local therapy (surgery and/or radiotherapy) and adjuvant chemotherapy + regional hyperthermia, or to the comparison group that received the same procedures without regional hyperthermia. The BSD-2000 device was used to deliver the hyperthermia. Table A16 – Appendix 4 – summarizes the hyperthermia treatment-related parameters for the EORTC RCT.

Median age at baseline was 52 years (range 18–70 years) and the gender distribution was 45% female and 55% male. The patients had large tumours with median tumour diameters of 11 cm (range 5–40 cm). Tumour grading at baseline was grade 2 for 47% of the patient population and grade 3 for 52%. The TNM stage was T2N0/1M0 and the AJCC prognostic stage group was IIIB. The trial included 44% tumours located in the extremities and 56% in the non-extremities. Disease status was primary for 48% of the patients, recurrent for 11% and 41% had prior surgery. Metastatic patients were excluded.

The overall judgement of the risk of bias for this study was high risk. Figure 9 provides a summary of the risk of bias assessment for the EORTC trial. Further details are available in the evidence table and the risk of bias tables included in Appendix 1.

Figure 9: Risk of bias summary for the EORTC trial



Mortality

[D0001] – What is the expected beneficial effect on mortality of non-invasive regional hyperthermia in addition to chemo- and or radiotherapy?

Overall survival was defined as time from randomisation to death from any cause. EORTC 2010 reported 44% deaths in the intervention group, 46% in the comparison group and an HR of 0.88 (95% CI 0.64, 1.21). The median survival duration was reported to be 6.6 years (95% CI 4.5, >10) in the intervention group versus 6.1 years (95% CI 3.8, >10) in the comparison group. The certainty of the evidence was rated as low, and the outcome as critical for decision-making.

EORTC 2018 reported 54% deaths in the intervention group versus 61% in the comparison group. No HR or time-to-event data were provided for overall survival. The certainty of the evidence was rated as low, and the outcome as critical for decision-making.

Disease-specific survival was defined as time from randomization to death due to disease or its treatment. EORTC 2018 reported disease-specific survival with a median duration of 15.4 years (95% CI 6.6, >17.0) in the intervention group and 6.2 years (95% CI 3.2, 10.3) in the comparison group with an HR of 0.73 (95% CI,0.54, 0.98). The proportion of patients with death from disease or treatment was 48% in the intervention group versus 58% in the comparison group. The certainty of the evidence was rated as low, and the outcome as critical for decision-making.

Survival rate at five years was 62.7% in the intervention group versus 51.3% in the comparison group (RD 11%, 95% CI 7, 16%). At five years, the survival rate was 62.7% in the intervention group and 51.3% in the comparison group (RD 11% (95% CI 1, 22%). Survival rate at 10 years was 53% in the intervention group versus 43% in the comparison group (RD 10% (95% CI -1, 21%).

Morbidity

[D0005] – How does non-invasive regional hyperthermia affect the symptoms and findings (severity, frequency) of STS?

The outcome objective response rate was defined as the number of patients with complete or partial response after induction therapy among patients with measurable disease (n=244). EORTC 2010 reported an objective response rate of 29% in the intervention group and 13% in the comparison group (RD 16%, 95% CI 6, 26%). EORTC 2018 reported 30% in the intervention group and 13% in the comparison group (RD 17%, 95% CI 7, 27%).

The certainty of the evidence was rated as low, and the outcome as important for decision-making.

[D0006] – How does non-invasive regional hyperthermia affect progression (or recurrence) of STS?

The disease-free survival outcome was defined as time from randomisation to confirmed local failure, distant metastases, or death due to disease or treatment, whichever occurred first. The certainty of the evidence was rated as low. The outcome was rated as important for both short and long-term endpoints and decision-making.
EORTC 2018 reported an HR of 0.71 (95% CI 0.55, 0.93). The median duration of disease-free survival was 2.8 years in the intervention group (95% CI 2.0, 4.9) and 1.5 years in the comparison group (95% CI 1.1, 2.1).

The proportion of patients with disease-free survival at two years was 58% in the intervention group and 44% in the comparison group (RD 14%, 95% CI 3, 24%). At four years, these proportions were 42% and 35%, respectively (RD 7%, 95% CI -3, 17%).

Progression-free survival was defined as time from randomisation to confirmed local progression, relapse, or death, whichever occurred first and irrespective of any occurrence of distant metastases.

EORTC 2018 reported an HR of 0.65 (95% CI 0.49, 0.86). The median duration of progression-free survival was 5.6 years (95% CI 2.9, 8.7) in the intervention group and 2.4 years (95% CI 1.7, 4.2) in the comparison group.

The proportion of patients with progression-free survival at two years was 76% in the intervention group and 61% in the comparison group (RD 15%, 95% CI 6, 25%). At four years, these proportions were 66% and 55%, respectively (RD 11%, 95% CI 1, 21%).

The studies did not measure the rate of local tumour control and local tumour recurrence outcomes. These outcomes were rated as important for decision-making.

[D0011] – What is the effect of non-invasive regional hyperthermia on patients' bodily functions?

We selected amputation as an outcome for this research question. This outcome was rated as low quality and as critical for decision-making.

EORTC 2010 reported that within the intervention group 7% required an amputation versus 9% in the comparison group (RD -2%, 95% CI -10%, 5%).

In EORTC 2018, there was 9% amputation in the intervention group versus 11% in the comparison group (RD -2%, 95% CI -11%, 7%).

Health-related quality of life

[D0012] – What is the effect of non-invasive regional hyperthermia on generic health-related quality of life?

The studies did not measure this outcome and we were unable to answer this research question. Health-related quality of life was rated as an important outcome for decision-making.

[D0013] – What is the effect of non-invasive regional hyperthermia on disease-specific quality of life?

The studies did not measure this outcome and we were unable to answer this research question. Disease-specific quality of life was rated as an important outcome for decision making.

Satisfaction

[D0017] – Were patients satisfied with non-invasive regional hyperthermia?

The studies did not measure this outcome and we were unable to answer this research question. Satisfaction was rated as an important outcome for decision-making.

Resource use – procedural time

The studies did not measure these outcomes and we were unable to answer these research questions. These outcomes were rated as an important outcome for decision-making.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?
C0002	What are the harms related to dosage or frequency of applying non-invasive regional hyperthermia?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed by the use of non-invasive regional hyperthermia?
B0010	What kind of data/records and/or registry is needed to monitor the use of non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?

6.2 Results

Included studies

For this domain we have used evidence from the EORTC RCT and evidence from ten single-arm trials.[28-31, 54-61] The single arm studies were published between 1995 and 2015 and included a median of 20 patients (range 6–97).

Most studies focused on curative treatment, except Uno 1995 and Volovat 2014, which focused on patients undergoing palliative treatment. The studies comprised patient groups with median and average ages in the 50s. Ages typically ranged from 18 to 80 years, with 89 years at the upper end. The studies included slightly more male (56%) than female patients (44%).

The studies included large tumours with diameters of over 5 cm for all or most of the patients.[28-30, 57, 58, 60] Other studies reported mean tumour volumes of 251 cm^3 and 1668 cm^3 or median volumes of 240 cc and 300 cc.[55-57, 59] In two studies, tumour size was not reported.[31, 54]

Tumour grading at baseline was grade 2 for 46% (n=249) of the patient population, grade 3 for 53% (n=286) and an unspecified high grade for 1% (n=4). Three studies did not provide information on tumour grading.[30, 59, 61]

Depth of the tumour and TNM stage were poorly reported across the included studies.

Overall, the studies included an equal number of tumours located in the extremities or non-extremities. Hayashi 2015 only included extremity tumours. Fiegl 2004 and Volovat 2014 only included non-extremity tumours.

Six studies included patients with non-metastatic disease.[29, 30, 55, 58-60] Three further studies stated that they had excluded patients with distant metastatic disease.[30, 56, 57] One study included patients with metastatic disease only.[61] Only one study included both metastatic and non-metastatic patients.[54]

Five studies applied hyperthermia in combination with chemotherapy and radiotherapy,[29, 31, 57, 59, 60] four studies applied hyperthermia combined with chemotherapy [54-56, 61] and two studies applied hyperthermia together with radiotherapy.[30, 58]

Four studies used hyperthermia as a neoadjuvant treatment,[30, 54, 55, 58] two studies used hyperthermia adjuvantly and three studies used hyperthermia both neoadjuvantly and adjuvantly.[29, 56, 57]

Eight studies used the BSD-2000 device,[29, 30, 54-58] two studies used the Thermotron RF-8,[31, 60] one study used both the BSD-1000 and the HEH-500C devices[59] and one study used the EHY-2000 device.[61] The BSD and EHY-2000 devices have CE approval but not the Thermotron RF-8 and HEH-500C devices. We did not identify eligible studies using other CE-approved devices.

All the studies targeted tumour temperatures within the predefined range, although two studies reported maximum temperatures above 50°C.[58, 59]

Table A16 – Appendix 4 – summarizes the hyperthermia treatment-related parameters of the included studies. Reporting on temperature and/or dosage was incomplete in most studies, apart from the study by Makihata 1997.[59] Two studies reported tumour temperatures ranges with upper values that were outside the internationally accepted quality assurance guidelines for regional hyperthermia.[58, 59]

EORTC 2010 reported on adverse events from the EORTC RCT related to chemotherapy and/or hyperthermia.[29] No data were available for adverse events related to surgery or radiotherapy. Prosnitz 1999, Maguire 2001, Uno 1995 and Volovat 2014 reported on adverse events for each treatment component. The other single-arm trials reported on hyperthermia-related adverse events and some of the other treatment components. Surgery-related adverse events were least reported. Some studies reported on acute toxicities only. Reporting on acute or late toxicity was generally poor.

Seven studies used the CTCAE grading system.[29, 31, 54-56, 60, 61] Maguire 2001 graded adverse events according to the guidelines of the Radiation Therapy Oncology Group (RTOG). Baur 2003 applied a non-defined grading system. Prosnitz 1999 and Makihata 1997 did not grade adverse events.[30, 55, 58, 59]

Follow-up times ranged from eight months to 17.6 years. For Maguire 2001 and Volovat 2014 the follow-up duration was not clear.[58, 61]

Further details of each study are available in evidence tables included in Appendix 1.

Patient safety

[C0008] – How safe is non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?

Death related to adverse events

EORTC 2018 reported that 3.1% of patients died because of adverse events in the EORTC RCT hyperthermia group and 1.2% in the comparison group (RD 2%, 95% CI -1, 5%) (Table 6-1).[28] Median follow-up was 11 years. The evidence was rated as low quality and critical for decision-making.

Prosnitz 1999 and Hayashi 2015 were the only single-arm trials to include data on deaths related to adverse event.[30, 31] In Prosnitz 1999, 3.1% (95% CI 1, 9%) of patients died from complications within a median follow-up period of 2.6 years (range 1–12.9 years). In Hayashi 2015, all patients were alive (95% CI 0, 46%) after a mean follow-up period of 10.9 years (range 8.1–17.6 years). The evidence was rated as very low quality and critical for decision-making.

Severe to life-threatening adverse events (grade 3 to 4)

EORTC 2010 reported grades 3–4 haematological toxicities, nephrotoxicities, cardiotoxicities, neurotoxicities, gastrointestinal toxicities, infections, musculoskeletal and connective tissue disorders, injuries and general disorders.[29] Frequencies for each type of toxicity and other adverse events are available in Table 6-2. Median follow-up was three years. The evidence was rated as very low quality and critical for decision-making.

All the single-arm trials reported severe adverse events in one or more of the following categories: haematological disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders, renal disorders, neurological disorders, general disorders, respiratory disorders, musculoskeletal and connective tissue disorders, infections, injuries and adverse events because of the pressure of the hyperthermia bolus. The evidence was rated as very low quality and critical for decision-making.

Maguire 2001 reported a mean of 0.23 severe to life-threatening acute adverse events per patient. There were no severe late adverse events (95% CI 0, 11%).[58]

Makihata 1997 found that 14% (95% CI 2, 43%) of patients had severe to life-threatening adverse events.[59]

In the study by Uno 1995, all patients 100% (95% CI 63, 100%) experienced a severe to life-threatening acute adverse event. The patients had on average 1.8 acute severe to life-threatening adverse events.[60]

Prosnitz 1999 reported that 4% (95% CI 1, 10%) of patients required amputation due to complications.[30] In Makihata 1997, the risk for amputation due to complications was 7% (95% CI 0.2, 34%).[59]

The evidence tables A2 and A3 in Appendix 1 provide further data on the occurrence of specific adverse events, also including data for the studies by Baur 2003, Fiegl 2004, Issels 2001 and Volovat 2014, for which no overall statements could be made about adverse events.

Mild to moderate adverse events (grades 1 to 2)

In Uno 1995, 100% of patients (95% CI 63, 100%) experienced mild to moderate acute adverse events.[60] In Makihata 1997, 57% of patients (95% CI 29, 82%) had mild to moderate adverse events as maximum toxicity.[59] Maguire 2001 reported a mean of 17 mild to moderate acute adverse events per 100 patients.[58] The evidence was rated as very low quality and not important for decision-making.

Any adverse events

Prosnitz 1999 reported that 39% of patients (95% CI 29, 50%) experienced adverse events.[30] Maguire 2001 found that 33% of patients (95% CI 17, 53%) experienced acute adverse events.[58]

Hayashi 2015 reported a mean of around 4.8 adverse events per patient, Prosnitz 1999 reported 1.5 adverse events per patient, Makihata 1997 encountered a mean of one adverse event per patient and Maguire 0.4 per patient.[30, 31, 58, 59]

The evidence derived from “any adverse events” was rated as very low quality and not given a rating for decision-making.

[C0002] – What are the harms related to dosage or frequency of applying non-invasive regional hyperthermia?

Maguire 2001 reported that no correlation was found between thermal dose and the development of treatment-induced toxicity (data were not shown).[58]

[C0004] – How does the frequency or severity of harms change over time or in different settings?

We did not identify evidence to answer the research question on the influence of different settings.

Fiegl 2004, Uno 1995 and Maguire 2001 included statements about acute toxicities.[54, 58, 60] Maguire 2001 was the only study to make reference to late toxicities. In the other studies, the data did not permit a confident assessment as to whether the complication was acute or late. In the discussion section, we elaborated on what was the most likely interpretation of the data for being acute or late.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of non-invasive regional hyperthermia?

We did not identify evidence to answer this research question.

[B0010] – What kind of data/records and/or registry is needed to monitor the use of non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?

The quality assurance guidelines for regional hyperthermia recognised by ESHO provided recommendations for documentation in studies on regional hyperthermia.[40] These include:

- Physical-technical documentation with data on the course of the treatment and hyperthermia device data.
- Clinical documentation on patient positioning, medication and clinical parameters of the patient and data on the side effects of the combined treatment and hyperthermia-specific side effects.

It should be noted that these ESHO statements are currently being updated. Our search did not retrieve any other studies that reported on specific data records or registries that should be used to monitor the use of regional hyperthermia.

Table 6-1: Frequency and severity of grades 1–5 adverse events in EORTC trial.

System organ/class/adverse events	Grade 5			
	Intervention (n = 162) n (%)	Comparator (n = 167) n (%)	Relative risk (95% CI)	Risk difference (95% CI)
Death related to any adverse event	5 (3.1%)	2 (1.2%)	2.58 (0.51, 13.09)	2% (-1, 5)
Adapted from European Public Assessment Reports published by the European Medicines Agency From tables 3a and 5 of the EUnetHTA safety guidelines				

Abbreviations: CI, confidence interval

Table 6-2: Frequency and severity of grades 1–4 adverse events in EORTC trial.

System organ/ class/adverse events	Grades 1–2				Grades 3–4			
	Intervention (n = 165) n (%)	Comparator (n = 167) n (%)	Relative risk (95% CI)	Risk difference (95% CI)	Intervention (n = 165) n (%)	Comparator (n = 167) n (%)	Relative risk (95% CI)	Risk difference (95% CI)
General disorders								
Fever of unknown origin					1 (0.6%)	5 (3.0%)	0.20 (0.02, 1.71)	-2% (-5, 0)
Pain[1]	66 (40.5%)	-			7 (4.3%)	-		
Haematological toxicities								
Acute leukaemia					3 (1.8%)	2 (1.2%)	1.52 (0.26, 8.97)	1% (-2, 3)
Leukopenia					128 (77.6%)	106 (63.5%)	1.22 (1.06, 1.41)	14% (4, 24)
Thrombocytopenia					28 (17.0%)	23 (13.8%)	1.23 (0.74, 2.05)	3% (-5, 11)
Neurotoxicities								

System organ/ class/adverse events	Grades 1–2				Grades 3–4			
	Intervention (n = 165) n (%)	Comparator (n = 167) n (%)	Relative risk (95% CI)	Risk difference (95% CI)	Intervention (n = 165) n (%)	Comparator (n = 167) n (%)	Relative risk (95% CI)	Risk difference (95% CI)
Not otherwise specified					15 (9.1%)	8 (4.8%)	1.90 (0.83, 4.35)	4% (-1, 10)
Gastrointestinal toxicities								
Nausea					23 (13.9%)	26 (15.6%)	0.90 (0.53, 1.50)	2% (-9, 6)
Vomiting					15 (9.1%)	9 (5.4%)	1.69 (0.76, 3.75)	4% (-2, 9)
Cardiotoxicities								
Not otherwise specified					3 (1.8%)	4 (2.4%)	0.76 (0.17, 3.34)	-1% (-4, 3)
Infections								
Localised infections[1]	5 (3.1%)	-			2 (1.2%)	-		
Injuries								
Skin burns[1]	29 (17.8%)	-			1 (0.6%)	-		
Musculoskeletal and connective tissue disorders								
Tissue necrosis[1]	7 (4.3%)	-			4 (2.5%)	-		
Others								
Bolus pressure[1]	43 (26.4%)	-			8 (4.9%)	-		
Claustrophobia, not power-related pain, wound healing disorder, nausea[1]	23 (14.1%)	-			14 (8.6%)	-		

1 The denominator for this adverse event was n=163.

Adapted from European Public Assessment Reports published by the European Medicines Agency.

From tables 3a and 5 of the EUnetHTA safety guidelines.

Abbreviations: CI, confidence interval

7 POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL, AND LEGAL ASPECTS (ETH, ORG, SOC, LEG)

Appendix 3 contains the completed checklist for potential ethical, organisational, patient and social, and legal aspects. To answer the checklist we used information derived from the literature search, web searches and clinical experts as information sources.

The checklist indicates that there could be ethical, organisational and legal aspects that users of this assessment report may wish to evaluate further. It was not our objective to provide an in-depth overview of each aspect.

8 DISCUSSION

Findings related to the health problem and the technology

Sarcomas are a rare and heterogeneous group of malignant tumours of mesenchymal origin. STSs can originate in all anatomic body sites, but mainly in the extremities. Sarcoma patients usually present a new or growing lump, which may be painless until it creates pressure on nerves or organs. Tumours located in the abdomen may obstruct and cause bleeding of the bowels or stomach. This can present as abdominal pain. The majority of new cases originate from soft tissue and the rest originate from bone. Sarcoma tumours are classified in different subtypes that can have very different clinical presentations, biological behaviours and prognoses. The most common symptoms are pain, paraesthesia or oedema in an extremity, generally associated with compression by the mass.

Relapse, side effects of treatment, disability due to surgery, psychological well-being of family and carers and other factors were reported as important post-treatment concerns that affected the overall treatment experience of STS patients. A recent systematic review identified the important financial and social impact on patients with a STS diagnosis.[170] As a rare disease, the financial impact is much higher for the individual patient than for society. Estimated per-patient lifetime medical costs show a wide variation across countries globally. Chapter 4 provides further information on this health problem.

Because of their rarity and the frequent need for multimodality treatment, the guidelines recommend that evaluation and management of STSs occur at a specialized centre with expertise in the treatment of sarcomas, including surgical oncology, orthopaedic surgery, plastic surgery, adult or paediatric medical oncology, radiation oncology, and a high volume of treated patients. Surgery is the first choice for all localised operable tumours, with the objective of obtaining a margin-negative resection. Unfortunately, surgical resection is not always achievable, particularly for high-risk STS patients. Thus, regional hyperthermia, combined with chemotherapy and radiotherapy, could have an emerging role as a limb-sparing technique for patients with high-risk STSs. Hyperthermia treatments use the biological effect of artificially induced heat that can be applied locally, regionally (superficial and deep) or as a whole-body treatment. The treatment is usually given at the same institution at which the other oncology treatments are performed, or at centres that can be reached within a short time frame. However, hyperthermia treatment can also be performed as outpatient therapies. To use regional hyperthermia, the treatment setting needs special premises which, in its broadest configuration, requires a treatment room, operator room and a small technical room.

Multiple manufacturers provide CE-approved devices in Europe. These manufacturers claim the following benefits of hyperthermia for cancer treatment in general: improved tumour control, remission rates and reduced risk of metastases; improved quality of life; higher success of treatment with chemotherapy, radiotherapy and surgery by destroying tumour cells and reducing tumour size; better long-term prognosis. Hyperthermia may also amplify immune responses in the body against cancer while decreasing the immune suppression and immune escape of cancer. This points at a potential for cancer therapy in conjunction with immunotherapy. Chapter 3 provides a further description of the technical characteristics of this technology.

Effectiveness and safety findings

We selected overall survival as the main endpoint for this assessment. In terms of overall survival, hyperthermia combined with chemotherapy and radiotherapy may not provide an important benefit versus chemotherapy and radiotherapy only. In the EORTC 2010 report, the point estimate for the hazard ratio did not reach the 0.80 ASCO threshold for clinical significance. The 95% confidence interval was wide and included both clinically relevant benefit and harm, which presents a large imprecision (95% CI 0.64, 1.21). The median survival time did not reach the 25% increase threshold. It is important to note that these data for overall survival are intermediate data. More than half of the patients were still alive in the comparison groups, implying that the authors did not yet know what the median value was and that the follow-up period in EORTC 2010 was too short to observe any effects from hyperthermia.

The EORTC 2018 did not report data on overall survival, but provided data on deaths and disease-specific survival. For deaths there was a risk difference of 7% (95% CI 2, 11), which indicates that less patients died when the treatment was combined with hyperthermia.

Disease-specific survival had a hazard ratio of 0.73 (95% CI 0.54, 0.98) and a difference in median survival time of 9.2 years (15.4 years in the intervention group and 6.2 years in the control group). The trial authors switched from reporting overall survival to disease-specific survival. In the EORTC 2018 paper, the authors state that their motivation to switch was because the 20-year data set included a large number of older patients at increased risk of death from other causes. This increased risk of death from other causes in aging trial populations is a complication in clinical research that has led to developments in competing risk methodology. Competing risks in medical research occur when the time to a disease-specific endpoint of interest may be precluded by death or a major health event from another cause.[33] EORTC 2018 estimated the survival outcomes according to the Kaplan-Meier method, but in the presence of competing risks this method is problematic and could lead to flawed effect estimates. In general, when survival outcomes are not accounted for competing risks, the results tend to be overestimated.[34] We would have liked to see the overall survival data for the long-term results together with the disease-specific survival data that were adjusted for competing risks. Looking at the causes of other deaths, around 4% of patients died from other causes in EORTC 2018. There are currently no guidelines regarding what magnitude of competing events is problematic and likely to result in biased estimations when analysed using conventional statistical methods.[34]

This failure to address competing risks may also have affected the results for progression-free survival and disease-free survival from EORTC 2018. Progression-free survival showed an important benefit for the median duration of progression-free survival of 3.2 years (5.6 years in the intervention group and 2.4 years in the control group). The hazard ratio was 0.65 (95% CI 0.49, 0.86). For disease-free survival, there was an HR of 0.71 with confidence intervals that point at both a small and an important benefit (95% CI 0.55, 0.93). The differences in median duration of disease-free survival was 1.3 years (2.8 years in the intervention group and 1.5 years in the control group).

EORTC 2010 and 2018 reported, respectively, a 7% and 9% risk of amputation in the hyperthermia group, with a broad 95% CI.

Deaths from adverse events were higher in the hyperthermia group with two more deaths per 100 patients (95% CI -1, 5%). Deaths from adverse events were reported in two single-arm studies and occurrence varied from 0% to 3%. In EORTC 2010, the authors hypothesized that this might

be due to bone marrow suppression. Thermosensitisation of neighbouring bone marrow in cases of large abdominal tumours may increase haematological toxicity from chemotherapy.

The EORTC trial reported severe to life-threatening adverse events in multiple clinical categories. Hyperthermia increased the risk of leukopenia with 14 more cases in 100 patients (95% CI 4, 24%) versus the comparison group. For the other toxicities, the 95% CI was wide, including values that pointed at both increased or reduced harm. Severe to life-threatening adverse events that were described as hyperthermia specific included localised infections (1.2%), burns (0.6%), tissue necrosis (2.5%), bolus pressure (4.9%) and other severe to life-threatening adverse events (including claustrophobia, nausea, wound healing disorders, pain) (8.6%). Severe to life-threatening adverse events were reported in all the single-arm studies, with occurrence ranging from 14% to 100%. Two studies reported a mean of 0.23 and 1.8 for severe to life-threatening adverse events per patient.[58, 60] Two single-arm studies reported amputations due to complications with risks varying from 4% to 7%.[30, 59] Reporting of acute/late toxicities was poor, although the clinical experts judged that late events likely occurred in at least eight studies and in the following categories: renal disorders, neurological disorders, cardiac disorders, musculoskeletal disorders, connective tissue disorders and injuries. Late events could also possibly have occurred as infections and general disorders.

The objective response rate was better for patients in the hyperthermia group with 17 patients out of 100 more with a complete or partial response (95% CI 7, 27%).

Evidence from only one RCT was available to evaluate the research questions from the effectiveness domain. We rated the certainty of the evidence for each of the outcomes of the effectiveness domain as low. This rating implies that our confidence in the effect estimate is limited and that the true effect may be substantially different from the estimate of the effect. We downgraded the certainty because of limitations in study design and imprecision. The limitations in study design included lack of blinding of the outcome assessors for the outcomes that require judgement and selective outcome reporting. While the EORTC trial protocol planned to evaluate overall survival, the EORTC 2018 paper only reported on disease-specific survival. We contacted the authors to obtain overall survival data, but we did not receive the data. We did not downgrade the certainty of the evidence based on indirectness in populations, interventions, comparisons or outcomes. The EORTC trial was sponsored by not-for- profit organisations and the trial reports transparently disclosed the role and responsibilities of the sponsors. However, some of the study authors have received support and honoraria from the industry. Such financial relationships are a general topic of concern that could bias the results.[209]

For the safety domain we had evidence from one RCT and from ten single-arm studies. We rated the certainty of the evidence as low for deaths from adverse events and very low for each of the other adverse event outcomes. This rating means that we have very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect. The reasons for downgrading the certainty were limitations in study design, inconsistency, imprecision, risk of publication bias and partial reporting of adverse events which do not cover all the treatment components.

Evidence gaps

The identified studies only partially match the predefined scope of this assessment. The majority of the studies focused on curative treatment. In most of the studies, metastatic patients were excluded. This makes it impossible to answer the research questions for this subset of patients.

On the intervention level, the studies evaluated devices from three manufacturers among which two produced CE-approved devices. The reporting on hyperthermia-related parameters was incomplete. Future studies should report hyperthermia intervention in accordance with the accepted quality assurance guidelines.

In this assessment the selection of the outcomes was informed by the research priorities formulated by the James Lind Alliance and we conducted a systematic process to rate the importance of the selected outcomes.[46] The available RCT reported on multiple outcomes that the assessment team considered critical for decision-making. The assessment team also rated additional outcomes as critical, i.e. health-related quality of life, pain – although these were not evaluated in the RCT. Other predefined outcomes that the assessment team rated as important for decision-making, i.e. fatigue, motor function, neurological function, psychological well-being, patient satisfaction, shared decision-making-related measures and resource use were not measured in the EORTC trial. Four studies reported on adverse events for each treatment component. The other studies reported on hyperthermia-related adverse events, but only partially covered adverse events that resulted from the other treatment components. Surgery-related adverse events were least reported. Some studies reported on acute toxicities only. Reporting on acute or late toxicity was generally poor. This implies that the presented data might be an underestimation. Future studies should focus on patient-important outcomes that are important for decision-making. Reporting on adverse events should focus on all treatment components and should cover both acute and late toxicities.

In order to close the present evidence gap, we need additional evidence. With the aim of minimising uncertainty about the effect estimates, we suggest striving for additional RCTs to allow informed decisions by HTA decision-makers. However, STS is a rare disease, making it inherently difficult to enrol patients to trials. The challenges related to evidence requirements for rare diseases need to be considered in the decision-making process.[210] Any future RCTs should plan for blinding of the outcome assessors for subjective outcomes and intention-to-treat analyses are needed for both effectiveness and safety outcomes. If disease-specific survival is analysed, we suggest adjustment for competing risks is carried out. We identified three ongoing studies, including one RCT that compares hyperthermia and chemotherapy to chemotherapy only and two single-arm trials. It is not clear when these studies will be completed. This assessment team is committed to updating the report once the results of these studies are available.

Relation to other assessments

The LBI-HTA 2012 health technology assessment concluded that the available evidence was insufficient to make a clear judgment of the effectiveness and safety of hyperthermia combined with radiotherapy and chemotherapy in the treatment of breast, bladder, uterine cervix carcinoma and STS.[42]

This current assessment included the same EORTC trial that was covered by the LBI-HTA 2012 assessment, but added the long-term results of this trial that were published by EORTC 2018. Furthermore, this assessment included the results of ten single-arm trials to provide additional information about adverse events. We did not find any prospective multiple-arm registry based studies that matched our scope.

On the methodological level, this current assessment applied the GRADE approach, including a rating of the importance of outcomes for decision-making, the identification of minimal important differences to guide interpretation of the magnitude of effects, the rating of the certainty of the evidence and the use of summary of findings tables.

Limitations of this assessment

Despite multiple attempts, we were not able to involve patient participants during the development of this assessment. This means that we did not have the patient perspective when rating the importance of the outcomes for decision-making.

Through a review of the evidence, web searches, contacts with clinical experts and manufacturers we identified four manufacturers that provide CE-approved devices for regional hyperthermia in Europe. A public database of CE-approved systems is lacking and we therefore acknowledge that there may be additional CE-approved systems available of which we are unaware.

The use of devices for regional hyperthermia requires the establishment of specialised centres of administration. This could create organisational and ethical issues due to reduced access for geographical reasons. From a legal perspective treatment with hyperthermia devices may require the use of a documented informed consent process. It was not the objective of this assessment to evaluate these aspects in detail and users of this assessment might want to evaluate these aspects further within their national or local context.

Hyperthermia is also used as a treatment method for other types of cancer. This assessment is limited to regional hyperthermia for high-risk STS. The findings of this review should not be extrapolated to other types of hyperthermia or other types of cancer.

9 CONCLUSION

Only one RCT assessed the effectiveness of this technology. It found improvements in disease-free survival, progression-free survival and disease-specific survival, but the analysis did not adjust for competing risk and the effect estimates may therefore be flawed. No important effects were found for the overall survival at short term, though the effect estimates were very imprecise, including both clinically meaningful benefit and harm. No long-term data on overall survival have been published. The certainty of the evidence was rated as low, meaning that further research is very likely to have an important impact, which is likely to change the estimate of effect.

Hyperthermia combined with chemotherapy and/or radiotherapy may lead to increased harm, including death by adverse events and severe leukopenia. The certainty of the evidence for the safety findings is rated as low for death from adverse events and very low for the other adverse events. Very low means that the estimates are very uncertain.

The currently available EORTC trial evaluated hyperthermia with a curative purpose that was administered both neoadjuvantty and adjuvantly. Another RCT is currently ongoing. Based on the information on inclusion criteria found in the trial registry for this HyperTET trial (NCT02359474), we anticipate that hyperthermia will be applied for both curative and palliative purposes. The curative treatment could include both a neoadjuvant and adjuvant application of hyperthermia.

The claimed benefits of hyperthermia for high-risk STS cannot be confirmed or rejected with the currently available evidence. Further research is needed to evaluate the effects of hyperthermia in various contexts, including neoadjuvant and adjuvant treatment, curative and palliative settings and for non-metastatic and metastatic disease. This research should also focus on overall survival, patient-important outcomes and should report on both acute and late adverse events for all treatment components. On the methods level, future research should incorporate blinding for outcome assessors and report clearly on any loss to follow-up and how these were handled. If disease-specific survival is analysed, we suggest that adjustment for competing risks is carried out.

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search for systematic reviews, HTAs and Guidelines

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 11, 2019
Search date: 2019-04-12

1 exp SARCOMA/ (133162)
2 exp Soft Tissue Neoplasms/ (23593)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcoma* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab,kw. (41398)
4 sarcom*.ti,ab,kw. (99473)
5 angiosarcoma*.ti,ab,kw. (5595)
6 Angioendotheliosarcoma*.ti,ab,kw. (4)
7 Chondrosarcoma*.ti,ab,kw. (7361)
8 Chondromucosarcoma*.ti,ab,kw. (0)
9 fibrosarcoma*.ti,ab,kw. (10865)
10 Dermatofibrosarcoma*.ti,ab,kw. (1798)
11 (bednar adj (tumour or tumor)).ti,ab,kw. (56)
12 (bednar's adj (tumour or tumor)).ti,ab,kw. (3)
13 Fibroblastoma*.ti,ab,kw. (280)
14 Darrier ferrand.ti,ab,kw. (4)
15 darier ferrand.ti,ab,kw. (57)
16 darier hoffmann.ti,ab,kw. (0)
17 Endotheliosarcoma*.ti,ab,kw. (12)
18 Neurofibrosarcoma*.ti,ab,kw. (386)
19 Haemangioendothelioma*.ti,ab,kw. (403)
20 Hemangioendothelioma*.ti,ab,kw. (2651)
21 Hemangiosarcoma*.ti,ab,kw. (994)
22 (Heart adj muscle adj (tumour* or tumor*)).ti,ab,kw. (0)
23 Haemangiosarcoma*.ti,ab,kw. (214)
24 Hemangiosarcoma*.ti,ab,kw. (0)
25 Histiosarcoma*.ti,ab,kw. (12)
26 histiocytoma*.ti,ab,kw. (5485)
27 kaposi*.ti,ab,kw. (14264)
28 Leiomyosarcoma*.ti,ab,kw. (9520)
29 Liposarcoma*.ti,ab,kw. (5878)
30 lymphangiosarcoma*.ti,ab,kw. (283)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab,kw. (329)
32 mpnst.ti,ab,kw. (1010)
33 Lymphangioendothelioma*.ti,ab,kw. (85)
34 (Mesodermal adj mixed adj (tumor* or tumour*)).ti,ab,kw. (82)
35 Myosarcoma*.ti,ab,kw. (151)
36 (Myocardial adj (tumour* or tumor*)).ti,ab,kw. (70)
37 (Myocardium adj (tumor* or tumour*)).ti,ab,kw. (1)

38 Rhabdomyosarcoma*.ti,ab,kw. (11141)
39 Myxosarcoma*.ti,ab,kw. (180)
40 Neurofibrosarcoma*.ti,ab,kw. (386)
41 Osteosarcoma*.ti,ab,kw. (21542)
42 Cystosarcoma*.ti,ab,kw. (584)
43 Phyllodes.ti,ab,kw. (1816)
44 (Rhabdoid adj (tumor* or tumour*)).ti,ab,kw. (1579)
45 (Small adj round adj cell adj (tumor* or tumour*)).ti,ab,kw. (1026)
46 Synovioma*.ti,ab,kw. (221)
47 Synoviasarcoma*.ti,ab,kw. (0)
48 Synoviosarcoma*.ti,ab,kw. (28)
49 Muscle neoplasm*.ti,ab,kw. (215)
50 Muscle cancer*.ti,ab,kw. (21)
51 Vascular neoplasm*.ti,ab,kw. (766)
52 vascular cancer*.ti,ab,kw. (47)
53 or/1-52 (235192)
54 exp Hyperthermia, Induced/ (30000)
55 hypertherm*.ti,ab,kw. (33113)
56 thermotherapy.ti,ab,kw. (2227)
57 fever therapy.ti,ab,kw. (173)
58 heat therapy.ti,ab,kw. (236)
59 diatherm*.ti,ab,kw. (3482)
60 diatherapy.ti,ab,kw. (1)
61 alba 4d.mp. (0)
62 celsius tcs.mp. (4)
63 synchroterm.mp. (0)
64 hydeep.mp. (0)
65 sigma-60.mp. (55)
66 bsd-2000.mp. (56)
67 bsd-500.mp. (0)
68 bsd medical.mp. (14)
69 or/54-68 (57073)
70 53 and 69 (1695)
71 Meta Analysis.pt. or "Meta-Analysis as Topic"/ or (Review.pt. and (pubmed or medline).ti,ab.) or ((systematic* or literature) adj3 (overview or review* or search*)).ti,ab,kf. or (meta-anal* or metaanal* or meta-regression* or umbrella review* or overview of reviews or review of reviews or (evidence* adj2 synth*) or synthesis review*).ti,ab,kf. (550994)
72 guideline*.ti,ab,kf. (311046)
73 Health Technology assessment.ti,ab,kw. (3865)
74 hta.ti,ab. (2679)
75 or/71-74 (827991)
76 70 and 75 (24)
77 limit 70 to "reviews (maximizes sensitivity)" (440)
78 limit 70 to guideline (0)
79 76 or 77 or 78 (445)
80 limit 79 to yr="1990 -Current" (388)

Database: Embase <1974 to 2019 April 11>

Search date: 2019-04-12

1 exp sarcoma/ (174875)
2 exp soft tissue tumor/ (51408)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcoma* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab. (57921)
4 sarcom*.ti,ab. (116959)
5 angiosarcoma*.ti,ab. (7275)
6 Angioendotheliosarcoma*.ti,ab. (2)
7 Chondrosarcoma*.ti,ab. (8951)
8 Chondromucosarcoma*.ti,ab. (0)
9 fibrosarcoma*.ti,ab. (12165)
10 Dermatofibrosarcoma*.ti,ab. (2362)
11 bednar tumor.ti,ab. (73)
12 bednar's tumor.ti,ab. (5)
13 Fibroblastoma*.ti,ab. (309)
14 Darrier ferrand.ti,ab. (7)
15 darier ferrand.ti,ab. (34)
16 darier hoffmann.ti,ab. (0)
17 Endotheliosarcoma*.ti,ab. (8)
18 Neurofibrosarcoma*.ti,ab. (413)
19 Haemangioendothelioma*.ti,ab. (516)
20 Hemangioendothelioma*.ti,ab. (3194)
21 Hemangiosarcoma*.ti,ab. (1094)
22 Heart muscle tumor*.ti,ab. (0)
23 Haemangiosarcoma*.ti,ab. (222)
24 Hemangiosarcoma*.ti,ab. (0)
25 Histiosarcoma*.ti,ab. (11)
26 histiocytoma*.ti,ab. (6435)
27 kaposi*.ti,ab. (16299)
28 Leiomyosarcoma*.ti,ab. (12051)
29 Liposarcoma*.ti,ab. (7801)
30 lymphangiosarcoma*.ti,ab. (273)
31 malignant peripheral nerve sheath tumour*.ti,ab. (443)
32 mpnst.ti,ab. (1520)
33 Lymphangioendothelioma*.ti,ab. (87)
34 Mesodermal mixed tumor*.ti,ab. (57)
35 Myosarcoma*.ti,ab. (144)
36 Myocardial tumor*.ti,ab. (83)
37 Myocardium tumor*.ti,ab. (5)
38 Rhabdomyosarcoma*.ti,ab. (14124)
39 Myxosarcoma*.ti,ab. (151)
40 Neurofibrosarcoma*.ti,ab. (413)
41 Osteosarcoma*.ti,ab. (27180)
42 Cystosarcoma*.ti,ab. (559)
43 Phyllodes.ti,ab. (2262)
44 Rhabdoid tumor*.ti,ab. (2526)
45 Small round cell tumor*.ti,ab. (1348)
46 Synovioma*.ti,ab. (83)
47 Synoviasarcoma*.ti,ab. (0)

48 Synoviosarcoma*.ti,ab. (32)
49 Muscle neoplasm*.ti,ab. (291)
50 Muscle cancer*.ti,ab. (37)
51 Vascular neoplasm*.ti,ab. (965)
52 vascular cancer*.ti,ab. (68)
53 or/1-52 (283440)
54 exp hyperthermia/ (26110)
55 hypertherm*.ti,ab. (39806)
56 thermotherapy.ti,ab. (2812)
57 fever therapy.ti,ab. (59)
58 heat therapy.ti,ab. (320)
59 diatherm*.ti,ab. (3895)
60 diatherapy.ti,ab. (1)
61 alba 4d.mp. (1)
62 celsius tcs.mp. (12)
63 synchroterm.mp. (0)
64 hydeep.mp. (0)
65 sigma-60.mp. (63)
66 bsd-2000.mp. (85)
67 bsd-500.mp. (10)
68 bsd medical.mp. (27)
69 or/54-68 (54287)
70 53 and 69 (1794)
71 "systematic review"/ (199184)
72 meta analysis/ (159894)
73 (((systematic* or literature) adj3 (overview or review* or search*)) or (meta-anal* or metaanal* or meta-regression* or umbrella review* or overview of reviews or review of reviews or (evidence* adj2 synth*) or synthesis review*)).ti,ab. (620136)
74 guideline*.ti,ab. (480878)
75 biomedical technology assessment/ (13458)
76 Health Technology assessment.ti,ab. (5094)
77 guideline*.ti,ab. (480878)
78 or/71-77 (1124616)
79 70 and 78 (53)
80 limit 70 to "reviews (maximizes sensitivity)" (427)
81 79 or 80 (444)
82 limit 81 to embase (325)
83 limit 82 to yr="1990 -Current" (249)

Database: Cochrane Database of Systematic Reviews
Search date: 2019-04-12
#1 MeSH descriptor: [Sarcoma] explode all trees 882
#2 MeSH descriptor: [Soft Tissue Neoplasms] explode all trees 209
#3 (((soft NEXT tissue*) or (soft NEXT part) or (connective NEXT tissue*) or (connective NEXT part)) and (sarcoma* or cancer* or neoplasm* or malignan* or tumor* OR tumour*)):ti,ab,kw 2125
#4 (sarcom* OR angiosarcoma* OR Angioendotheliosarcoma* OR Chondrosarcoma* OR Chondromucosarcoma* OR fibrosarcoma* OR Dermatofibrosarcoma* OR "bednar tumor" OR "bednar tumour" OR "bednar's tumour" OR "bednar's tumour" OR Fibroblastoma* OR "Darrier ferrand" OR

"darier ferrand" OR "darier hoffmann" OR Endotheliosarcoma* OR Neurofibrosarcoma* OR Haemangioendothelioma* OR Hemangioendothelioma* OR Hemangiosarcoma* OR "Heart muscle tumour" OR "heart muscle tumour" OR "Heart muscle tumours" OR "heart muscle tumours" OR Haemangiosarcoma* OR Hemangiosarcoma* OR Histiosarcoma* OR histiocytoma* OR kaposi* OR Leiomyosarcoma* OR Liposarcoma* OR lymphangiosarcoma* OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumours" OR "malignant peripheral nerve sheath tumours" OR mpnst OR Lymphangioendothelioma* OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumours" OR "Mesodermal mixed tumours" OR Myosarcoma* OR "Myocardial tumour" OR "Myocardial tumour" OR "Myocardial tumours" OR "Myocardium tumour" OR "Myocardium tumour" OR "Myocardium tumours" OR "Myocardium tumours" OR Rhabdomyosarcoma* OR Myxosarcoma* OR Neurofibrosarcoma* OR Osteosarcoma* OR Cystosarcoma* OR Phyllodes OR "Rhabdoid tumour" OR "Rhabdoid tumour" OR "Rhabdoid tumours" "Rhabdoid tumours" OR "Small round cell tumour" OR "Small round cell tumour" OR "Small round cell tumours" OR "Small round cell tumours" OR Synovioma* OR Synoviasarcoma* OR Synoviosarcoma* OR "Muscle neoplasm" OR "Muscle neoplasms" OR "Muscle cancer" OR "Muscle cancers" OR "Vascular neoplasm" OR "Vascular neoplasms" OR "vascular cancer" OR "vascular cancers"):ti,ab,kw 3304

#5 #1 OR #2 OR #3 OR #4 4431

#6 MeSH descriptor: [Hyperthermia, Induced] explode all trees 1513

#7 hypertherm* OR thermotherapy OR "fever therapy" OR "heat therapy" OR diatherm* OR diatherapy OR "alba 4d" OR "celsius tcs" OR synchroterm OR hydeep OR sigma-60 OR bsd-2000 OR bsd-500 OR "bsd medical":ti,ab,kw 3244

#8 #6 OR #7 4098

#9 #5 AND #8 in Cochrane Reviews, Cochrane Protocols 0

Database: AMED (Allied and Complementary Medicine) <1985 to April 2019>
Search date: 2019-04-12

1 exp Hyperthermia induced/ (122)
2 hypertherm*.ti,ab. (162)
3 thermotherapy.ti,ab. (40)
4 fever therapy.ti,ab. (5)
5 heat therapy.ti,ab. (14)
6 diatherm*.ti,ab. (94)
7 diatherapy.ti,ab. (0)
8 alba 4d.mp. (0)
9 celsius tcs.mp. (0)
10 synchroterm.mp. (0)
11 hydeep.mp. (0)
12 sigma-60.mp. (0)
13 bsd-2000.mp. (0)
14 bsd-500.mp. (0)
15 bsd medical.mp. (0)
16 or/1-15 (340)
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (340)
18 limit 17 to yr="1990 -Current" (315)

Database: Epistemonikos
Search date: 2019-04-12

(title:(hypertherm* OR thermotherapy OR "fever therapy" OR "heat therapy" OR diatherm* OR diatherapy OR alba-4d OR celsius-tcs OR syncroterm* OR hydeep OR sigma-60 OR bsd-2000 OR bsd-500 OR bsd-medical) OR abstract:(hypertherm* OR thermotherapy OR "fever therapy" OR" heat therapy" OR diatherm* OR diatherapy OR alba-4d OR celsius-tcs OR syncroterm* OR hydeep OR sigma-60 OR bsd-2000 OR bsd-500 OR bsd-medical)) AND (title:((sarcom* OR angiosarcoma* OR Angioendotheliosarcoma* OR Chondrosarcoma* OR Chondromucosarcoma* OR fibrosarcoma* OR Dermatofibrosarcoma* OR "bednar tumour" OR "bednar tumour" OR "bednar's tumour" OR "bednar's tumour" OR Fibroblastoma* OR "Darrier ferrand" OR "darier ferrand" OR "darier hoffmann" OR Endotheliosarcoma* OR Neurofibrosarcoma* OR Haemangioendothelioma* OR Hemangioendothelioma* OR Hemangiosarcoma* OR "heart muscle tumour" OR "Heart muscle tumour" OR "Heart muscle tumours" OR "heart muscle tumours" OR Haemangiosarcoma* OR Hermangiosarcoma* OR Histiosarcoma* OR histiocytoma* OR kaposi* OR Leiomyosarcoma* OR Liposarcoma* OR lymphangiosarcoma* OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumours" OR "malignant peripheral nerve sheath tumours" OR mpnst OR Lymphangioendothelioma* OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumours" OR "Mesodermal mixed tumours" OR Myosarcoma* OR "Myocardial tumour" OR "Myocardial tumour" OR "Myocardial tumours" OR "Myocardium tumour" OR "Myocardium tumour" OR "Myocardium tumours" OR "Myocardium tumours" OR Rhabdomyosarcoma* OR Myxosarcoma* OR Neurofibrosarcoma* OR Osteosarcoma* OR Cystosarcoma* OR Phyllodes OR "Rhabdoid tumour" OR "Rhabdoid tumour" OR "Rhabdoid tumours" OR "Rhabdoid tumours" OR "Small round cell tumour" OR "Small round cell tumour" OR "Small round cell tumours" OR "Small round cell tumours" OR Synovioma* OR Synoviasarcoma* OR Synoviosarcoma* OR "Muscle neoplasm" OR "Muscle neoplasms" OR "Muscle cancer" OR "Muscle cancers" OR "Vascular neoplasm" OR "Vascular neoplasms" OR "vascular cancer" OR "vascular cancers")) OR abstract:((sarcom* OR angiosarcoma* OR Angioendotheliosarcoma* OR Chondrosarcoma* OR Chondromucosarcoma* OR fibrosarcoma* OR Dermatofibrosarcoma* OR "bednar tumour" OR " bednar tumour" OR "bednar's tumour" OR "bednar's tumour" OR Fibroblastoma* OR "Darrier ferrand" OR "darier ferrand" OR "darier hoffmann" OR Endotheliosarcoma* OR Neurofibrosarcoma* OR Haemangioendothelioma* OR Hemangioendothelioma* OR Hemangiosarcoma* OR " heart muscle tumour" OR "Heart muscle tumour" OR "Heart muscle tumours" OR "heart muscle tumours" OR Haemangiosarcoma* OR Hermangiosarcoma* OR Histiosarcoma* OR histiocytoma* OR kaposi* OR Leiomyosarcoma* OR Liposarcoma* OR lymphangiosarcoma* OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumours" OR "malignant peripheral nerve sheath tumours" OR mpnst OR Lymphangioendothelioma* OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumours" OR "Mesodermal mixed tumours" OR Myosarcoma* OR "Myocardial tumour" OR "Myocardial tumour" OR "Myocardial tumours" OR "Myocardial tumours" OR "Myocardium tumour" OR "Myocardium tumour" OR "Myocardium tumours" OR "Myocardium tumours" OR Rhabdomyosarcoma* OR Myxosarcoma* OR Neurofibrosarcoma* OR Osteosarcoma* OR Cystosarcoma* OR Phyllodes OR "Rhabdoid tumour" OR "Rhabdoid tumour" OR "Rhabdoid tumours" OR "Rhabdoid tumours" OR "Small round cell tumour" OR "Small round cell tumour" OR "Small round cell tumours" OR "Small round cell tumours" OR Synovioma* OR Synoviasarcoma* OR Synoviosarcoma* OR "Muscle neoplasm" OR "Muscle neoplasms" OR "Muscle cancer" OR "Muscle cancers" OR "Vascular neoplasm" OR "Vascular neoplasms" OR "vascular cancer" OR "vascular cancers"))) (0 broad syntheses, 3 structured summaries, 3 systematic reviews)

Database: PROSPERO
Search date: 2019-04-12
Hyperthermia: 38

Thermotherapy: 22

Database: POP-database
Search date: 2019-04-12
Hyperthermia: 2
Thermotherapy: 0

Database: HTAi Vortal
Search date: 2019-04-25
Hyperthermia Sarcoma: 10
Thermotherapy Sarcoma: 15

Database: Guidelines International Network (G-I-N)
Search date: 2019-04-12
Hyperthermia: 2
Thermotherapy: 0

Database: NICE guidance
Search date: 2019-04-12
Hyperthermia: 12
Thermotherapy: 12

Database: NIHR-HTA
Search date: 2019-04-12
Hyperthermia: 1
Thermotherapy: 0

Database: Devices @FDA
Search date: 2019-04-12
Hyperthermia: 23
Thermotherapy: 7

Search for primary studies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 12, 2019>
Search date: 2019-04-15
1 exp SARCOMA/ (133169)
2 exp Soft Tissue Neoplasms/ (23595)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab,kw. (43803)
4 sarcom*.ti,ab,kw,kf. (103862)
5 angiosarcoma*.ti,ab,kw. (5879)
6 Angioendotheliosarcoma*.ti,ab,kw. (4)
7 Chondrosarcoma*.ti,ab,kw. (7571)
8 Chondromucosarcoma*.ti,ab,kw. (0)
9 fibrosarcoma*.ti,ab,kw. (11369)
10 Dermatofibrosarcoma*.ti,ab,kw. (1817)
11 (bednar adj (tumour or tumor)).ti,ab,kw. (68)
12 (bednar's adj (tumor or tumour)).ti,ab,kw. (5)
13 Fibroblastoma*.ti,ab,kw. (280)
14 Darrier ferrand.ti,ab,kw. (4)
15 darier ferrand.ti,ab,kw. (57)

16 darier hoffmann.ti,ab,kw. (0)
17 Endotheliosarcoma*.ti,ab,kw. (12)
18 Neurofibrosarcoma*.ti,ab,kw. (394)
19 Haemangioendothelioma*.ti,ab,kw. (403)
20 Hemangioendothelioma*.ti,ab,kw. (2769)
21 Hemangiosarcoma*.ti,ab,kw. (1025)
22 (Heart adj muscle adj (tumor* or tumour*)).ti,ab,kw. (0)
23 Haemangiosarcoma*.ti,ab,kw. (214)
24 Hemangiosarcoma*.ti,ab,kw. (1025)
25 Histiosarcoma*.ti,ab,kw. (12)
26 histiocytoma*.ti,ab,kw. (5488)
27 kaposi*.ti,ab,kw. (14382)
28 Leiomyosarcoma*.ti,ab,kw. (9745)
29 Liposarcoma*.ti,ab,kw. (6001)
30 lymphangiosarcoma*.ti,ab,kw. (304)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab,kw. (2062)
32 mpnst.ti,ab,kw. (1035)
33 Lymphangioendothelioma*.ti,ab,kw. (96)
34 Mesodermal mixed tumor*.ti,ab,kw. (84)
35 Myosarcoma*.ti,ab,kw. (178)
36 (Myocardial adj (tumour* or tumor*)).ti,ab,kw. (76)
37 (Myocardium adj (tumour* or tumor*)).ti,ab,kw. (2)
38 Rhabdomyosarcoma*.ti,ab,kw. (11335)
39 Myxosarcoma*.ti,ab,kw. (248)
40 Neurofibrosarcoma*.ti,ab,kw. (394)
41 Osteosarcoma*.ti,ab,kw. (21650)
42 Cystosarcoma*.ti,ab,kw. (628)
43 Phyllodes.ti,ab,kw. (1819)
44 Rhabdoid tumor*.ti,ab,kw. (1593)
45 (Small adj round adj cell adj (tumour* or tumor*)).ti,ab,kw. (1192)
46 Synovioma*.ti,ab,kw. (341)
47 Synoviasarcoma*.ti,ab,kw. (0)
48 Synoviosarcoma*.ti,ab,kw. (28)
49 Muscle neoplasm*.ti,ab,kw. (220)
50 Muscle cancer*.ti,ab,kw. (21)
51 Vascular neoplasm*.ti,ab,kw. (800)
52 vascular cancer*.ti,ab,kw. (47)
53 or/1-52 (238094)
54 exp Hyperthermia, Induced/ (30001)
55 hypertherm*.ti,ab. (33132)
56 thermotherap*.ti,ab. (2227)
57 fever therap*.ti,ab. (173)
58 heat therap*.ti,ab. (236)
59 diatherm*.ti,ab. (3482)
60 diatherap*.ti,ab. (1)
61 alba 4d.mp. (0)
62 celsius tcs.mp. (4)
63 synchroterm.mp. (0)
64 hydeep.mp. (0)
65 sigma-60.mp. (55)
66 bsd-2000.mp. (56)
67 bsd-500.mp. (0)
68 bsd medical.mp. (14)
69 or/54-68 (57092)
70 53 and 69 (1717)
71 limit 70 to yr="1990 -Current" (1229)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to September 04, 2019> Search including additional device terms

Search date: 2019-09-05

1 exp SARCOMA/ (134593)
2 exp Soft Tissue Neoplasms/ (23918)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab,kw. (45617)
4 sarcom*.ti,ab,kw,kf. (106724)
5 angiosarcoma*.ti,ab,kw. (6126)
6 Angioendotheliosarcoma*.ti,ab,kw. (4)
7 Chondrosarcoma*.ti,ab,kw. (7784)
8 Chondromucosarcoma*.ti,ab,kw. (0)
9 fibrosarcoma*.ti,ab,kw. (11495)
10 Dermatofibrosarcoma*.ti,ab,kw. (1878)
11 (bednar adj (tumour or tumor)).ti,ab,kw. (68)
12 (bednar's adj (tumor or tumour)).ti,ab,kw. (5)
13 Fibroblastoma*.ti,ab,kw. (287)
14 Darrier ferrand.ti,ab,kw. (4)
15 darier ferrand.ti,ab,kw. (59)
16 darier hoffmann.ti,ab,kw. (0)
17 Endotheliosarcoma*.ti,ab,kw. (12)
18 Neurofibrosarcoma*.ti,ab,kw. (400)
19 Haemangioendothelioma*.ti,ab,kw. (411)
20 Hemangioendothelioma*.ti,ab,kw. (2866)
21 Hemangiosarcoma*.ti,ab,kw. (1053)
22 (Heart adj muscle adj (tumor* or tumour*)).ti,ab,kw. (0)
23 Haemangiosarcoma*.ti,ab,kw. (217)
24 Hemangiosarcoma*.ti,ab,kw. (1053)
25 Histiosarcoma*.ti,ab,kw. (12)
26 histiocytoma*.ti,ab,kw. (5568)
27 kaposi*.ti,ab,kw. (14608)
28 Leiomyosarcoma*.ti,ab,kw. (10045)
29 Liposarcoma*.ti,ab,kw. (6243)
30 lymphangiosarcoma*.ti,ab,kw. (309)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab,kw. (2186)
32 mpnst.ti,ab,kw. (1112)
33 Lymphangioendothelioma*.ti,ab,kw. (99)
34 Mesodermal mixed tumor*.ti,ab,kw. (84)
35 Myosarcoma*.ti,ab,kw. (178)
36 (Myocardial adj (tumour* or tumor*)).ti,ab,kw. (77)
37 (Myocardium adj (tumour* or tumor*)).ti,ab,kw. (2)
38 Rhabdomyosarcoma*.ti,ab,kw. (11574)
39 Myxosarcoma*.ti,ab,kw. (251)
40 Neurofibrosarcoma*.ti,ab,kw. (400)
41 Osteosarcoma*.ti,ab,kw. (22304)
42 Cystosarcoma*.ti,ab,kw. (636)
43 Phyllodes.ti,ab,kw. (1889)
44 Rhabdoid tumor*.ti,ab,kw. (1654)
45 (Small adj round adj cell adj (tumour* or tumor*)).ti,ab,kw. (1228)
46 Synovioma*.ti,ab,kw. (343)
47 Synoviasarcoma*.ti,ab,kw. (0)

48 Synoviosarcoma*.ti,ab,kw. (29)
49 Muscle neoplasm*.ti,ab,kw. (228)
50 Muscle cancer*.ti,ab,kw. (21)
51 Vascular neoplasm*.ti,ab,kw. (850)
52 vascular cancer*.ti,ab,kw. (48)
53 or/1-52 (243683)
54 oncotherm*.ti,ab,kw. (16)
55 ehy-2000.ti,ab,kw. (0)
56 ehy-2030.ti,ab,kw. (0)
57 ehy-3010.ti,ab,kw. (0)
58 meht.ti,ab,kw. (78)
59 modulated electro-hyperthermia.ti,ab,kw. (19)
60 or/54-59 (91)
61 53 and 60 (4)
62 limit 61 to yr="1990 -Current" (4)

Database: Embase <1974 to 2019 April 12>
Search date: 2019-04-15
1 exp sarcoma/ (174947)
2 exp soft tissue tumor/ (51427)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab. (60479)
4 sarcom*.ti,ab. (116992)
5 angiosarcoma*.ti,ab. (7283)
6 Angioendotheliosarcoma*.ti,ab. (2)
7 Chondrosarcoma*.ti,ab. (8951)
8 Chondromucosarcoma*.ti,ab. (0)
9 fibrosarcoma*.ti,ab. (12166)
10 Dermatofibrosarcoma*.ti,ab. (2362)
11 (bednar adj (tumor or tumour)).ti,ab. (87)
12 (bednar's adj (tumor or tumour*)).ti,ab. (6)
13 Fibroblastoma*.ti,ab. (309)
14 Darrier ferrand.ti,ab. (7)
15 darier ferrand.ti,ab. (34)
16 darier hoffmann.ti,ab. (0)
17 Endotheliosarcoma*.ti,ab. (8)
18 Neurofibrosarcoma*.ti,ab. (413)
19 Haemangioendothelioma*.ti,ab. (516)
20 Hemangioendothelioma*.ti,ab. (3196)
21 Hemangiosarcoma*.ti,ab. (1094)
22 (Heart adj muscle adj (tumor* or tumour*)).ti,ab. (0)
23 Haemangiosarcoma*.ti,ab. (222)
24 Hermangiosarcoma*.ti,ab. (0)
25 Histiosarcoma*.ti,ab. (11)
26 histiocytoma*.ti,ab. (6437)
27 kaposi*.ti,ab. (16304)
28 Leiomyosarcoma*.ti,ab. (12056)
29 Liposarcoma*.ti,ab. (7806)
30 lymphangiosarcoma*.ti,ab. (273)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab. (2766)
32 mpnst.ti,ab. (1520)
33 Lymphangioendothelioma*.ti,ab. (87)
34 (Mesodermal adj mixed adj (tumor* or tumour*)).ti,ab. (66)
35 Myosarcoma*.ti,ab. (144)
36 (Myocardial adj (tumor* or tumour*)).ti,ab. (90)
37 (Myocardium adj (tumor* or tumour*)).ti,ab. (6)

38 Rhabdomyosarcoma*.ti,ab. (14125)
39 Myxosarcoma*.ti,ab. (151)
40 Neurofibrosarcoma*.ti,ab. (413)
41 Osteosarcoma*.ti,ab. (27185)
42 Cystosarcoma*.ti,ab. (559)
43 Phyllodes.ti,ab. (2262)
44 (Rhabdoid adj (tumor* or tumour*)).ti,ab. (2915)
45 (Small adj round adj cell adj (tumor* or tumour*)).ti,ab. (1553)
46 Synovioma*.ti,ab. (83)
47 Synoviasarcoma*.ti,ab. (0)
48 Synoviosarcoma*.ti,ab. (32)
49 Muscle neoplasm*.ti,ab. (291)
50 Muscle cancer*.ti,ab. (37)
51 Vascular neoplasm*.ti,ab. (966)
52 vascular cancer*.ti,ab. (68)
53 or/1-52 (286121)
54 exp hyperthermia/ (26120)
55 hypertherm*.ti,ab. (39829)
56 thermotherap*.ti,ab. (2813)
57 fever therap*.ti,ab. (59)
58 heat therap*.ti,ab. (320)
59 diatherm*.ti,ab. (3897)
60 diatherap*.ti,ab. (1)
61 alba 4d.mp. (1)
62 celsius tcs.mp. (12)
63 synchroterm.mp. (0)
64 hydeep.mp. (0)
65 sigma-60.mp. (63)
66 bsd-2000.mp. (85)
67 bsd-500.mp. (10)
68 bsd medical.mp. (27)
69 or/54-68 (54323)
70 53 and 69 (1812)
71 limit 70 to yr="1990 -Current" (1414)

Database: Embase <1974 to 2019 September 04> Search including additional device terms
Search date: 2019-09-05

1 exp sarcoma/ (179689)
2 exp soft tissue tumor/ (53102)
3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab. (62844)
4 sarcom*.ti,ab. (120162)
5 angiosarcoma*.ti,ab. (7510)
6 Angioendotheliosarcoma*.ti,ab. (2)
7 Chondrosarcoma*.ti,ab. (9190)
8 Chondromucosarcoma*.ti,ab. (0)
9 fibrosarcoma*.ti,ab. (12324)
10 Dermatofibrosarcoma*.ti,ab. (2425)
11 (bednar adj (tumor or tumour)).ti,ab. (88)
12 (bednar's adj (tumor or tumour*)).ti,ab. (6)
13 Fibroblastoma*.ti,ab. (311)
14 Darrier ferrand.ti,ab. (7)
15 darier ferrand.ti,ab. (36)
16 darier hoffmann.ti,ab. (0)
17 Endotheliosarcoma*.ti,ab. (8)
18 Neurofibrosarcoma*.ti,ab. (416)
19 Haemangioendothelioma*.ti,ab. (529)
20 Hemangioendothelioma*.ti,ab. (3281)
21 Hemangiosarcoma*.ti,ab. (1122)
22 (Heart adj muscle adj (tumor* or tumour*)).ti,ab. (0)
23 Haemangiosarcoma*.ti,ab. (228)

24 Hermangiosarcoma*.ti,ab. (0)
25 Histiosarcoma*.ti,ab. (11)
26 histiocytoma*.ti,ab. (6507)
27 kaposi*.ti,ab. (16643)
28 Leiomyosarcoma*.ti,ab. (12372)
29 Liposarcoma*.ti,ab. (8056)
30 lymphangiosarcoma*.ti,ab. (276)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab. (2895)
32 mpnst.ti,ab. (1591)
33 Lymphangioendothelioma*.ti,ab. (89)
34 (Mesodermal adj mixed adj (tumor* or tumour*)).ti,ab. (66)
35 Myosarcoma*.ti,ab. (146)
36 (Myocardial adj (tumor* or tumour*)).ti,ab. (91)
37 (Myocardium adj (tumor* or tumour*)).ti,ab. (6)
38 Rhabdomyosarcoma*.ti,ab. (14506)
39 Myxosarcoma*.ti,ab. (153)
40 Neurofibrosarcoma*.ti,ab. (416)
41 Osteosarcoma*.ti,ab. (28219)
42 Cystosarcoma*.ti,ab. (563)
43 Phyllodes.ti,ab. (2330)
44 (Rhabdoid adj (tumor* or tumour*)).ti,ab. (3043)
45 (Small adj round adj cell adj (tumor* or tumour*)).ti,ab. (1586)
46 Synovioma*.ti,ab. (83)
47 Synoviasarcoma*.ti,ab. (0)
48 Synoviosarcoma*.ti,ab. (33)
49 Muscle neoplasm*.ti,ab. (301)
50 Muscle cancer*.ti,ab. (38)
51 Vascular neoplasm*.ti,ab. (998)
52 vascular cancer*.ti,ab. (71)
53 or/1-52 (294208)
54 onco hyperthermia device/ (60)
55 oncotherm*.ti,ab. (31)
56 ehy-2000.ti,ab. (4)
57 ehy-2030.ti,ab. (1)
58 ehy-3010.ti,ab. (0)
59 meht.ti,ab. (87)
60 modulated electro-hyperthermia.ti,ab. (46)
61 or/54-60 (159)
62 53 and 61 (10)
63 limit 62 to yr="1990 -Current" (10)

Database: AMED (Allied and Complementary Medicine) <1985 to April 2019>
Search date: 2019-04-15

1 exp Hyperthermia induced/ (122)
2 hypertherm*.ti,ab. (162)
3 thermotherap*.ti,ab. (40)
4 fever therap*.ti,ab. (5)
5 heat therap*.ti,ab. (14)
6 diatherm*.ti,ab. (94)
7 diatherap*.ti,ab. (0)
8 alba 4d.mp. (0)
9 celsius tcs.mp. (0)
10 synchroterm.mp. (0)
11 hydeep.mp. (0)
12 sigma-60.mp. (0)
13 bsd-2000.mp. (0)
14 bsd-500.mp. (0)
15 bsd medical.mp. (0)
16 or/1-15 (340)
17 limit 16 to yr="1990 -Current" (315)

Database: AMED (Allied and Complementary Medicine) <1985 to August 2019> Search including additional device terms
Search date: 2019-09-05

1 oncotherm*.ti,ab. (1)
2 ehy-2000.ti,ab. (0)
3 ehy-2030.ti,ab. (0)
4 ehy-3010.ti,ab. (0)
5 meht.ti,ab. (0)
6 modulated electro-hyperthermia.ti,ab. (0)
7 or/1-6 (1)
8 limit 7 to yr="1990 -Current" (1)

Database: Cochrane Central Register of Controlled Trials
Search date: 2019-04-15

#1 MeSH descriptor: [Sarcoma] explode all trees 882
#2 MeSH descriptor: [Soft Tissue Neoplasms] explode all trees 209
#3 (((soft NEXT tissue*) or (soft NEXT part) or (connective NEXT tissue*) or (connective NEXT part)) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* OR tumour*)) 2457
#4 (sarcom* OR angiosarcoma* OR Angioendotheliosarcoma* OR Chondrosarcoma* OR Chondromucosarcoma* OR fibrosarcoma* OR Dermatofibrosarcoma* OR "bednar tumor" OR "bednar tumour" OR "bednar's tumour" OR "bednar's tumor" OR Fibroblastoma* OR "Darrier ferrand" OR "darier ferrand" OR "darier hoffmann" OR Endotheliosarcoma* OR Neurofibrosarcoma* OR Haemangioendothelioma* OR Hemangioendothelioma* OR Hemangiosarcoma* OR "Heart muscle tumor" OR "heart muscle tumour" OR "Heart muscle tumors" OR "heart muscle tumours" OR Haemangiosarcoma* OR Hemangiosarcoma* OR Histiosarcoma* OR histiocytoma* OR kaposi* OR Leiomyosarcoma* OR Liposarcoma* OR lymphangiosarcoma* OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumor" OR "malignant peripheral nerve sheath tumours" OR "malignant peripheral nerve sheath tumors" OR mpnst OR Lymphangioendothelioma* OR "Mesodermal mixed tumor" OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumors" OR "Mesodermal mixed tumours" OR Myosarcoma* OR "Myocardial tumor" OR "Myocardial tumour" OR "Myocardial tumors" OR "Myocardium tumor" OR "Myocardium tumour" OR "Myocardium tumors" OR "Myocardium tumours" OR Rhabdomyosarcoma* OR Myxosarcoma* OR Neurofibrosarcoma* OR Osteosarcoma* OR Cystosarcoma* OR Phyllodes OR "Rhabdoid tumor" OR "Rhabdoid tumour" OR "Rhabdoid tumors" "Rhabdoid tumours" OR "Small round cell tumor" OR "Small round cell tumour" OR "Small round cell tumors" OR "Small round cell tumours" OR Synovioma* OR Synoviasarcoma* OR Synoviosarcoma* OR "Muscle neoplasm" OR "Muscle neoplasms" OR "Muscle cancer" OR "Muscle cancers" OR "Vascular neoplasm" OR "Vascular neoplasms" OR "vascular cancer" OR "vascular cancers") 3555
#5 #1 OR #2 OR #3 OR #4 4965
#6 MeSH descriptor: [Hyperthermia, Induced] explode all trees 1513
#7 hypertherm* OR thermotherapy OR "fever therapy" OR "heat therapy" OR diatherm* OR diatherapy OR "alba 4d" OR "celsius tcs" OR synchroterm OR hydeep OR sigma-60 OR bsd-2000 OR bsd-500 OR "bsd medical" 3244
#8 #6 OR #7 4098
#9 #5 AND #8 in Trials 78

Database: Cochrane Central Register of Controlled Trials Search including additional device terms
Search date: 2019-09-05

#1 MeSH descriptor: [Sarcoma] explode all trees 900
#2 MeSH descriptor: [Soft Tissue Neoplasms] explode all trees 212
#3 (((soft NEXT tissue*) or (soft NEXT part) or (connective NEXT tissue*) or (connective NEXT part)) and (sarcoma* or cancer* or neoplasm* or malignan* or tumor* OR tumour*)) 2543
#4 (sarcom* OR angiosarcoma* OR Angioendotheliosarcoma* OR Chondrosarcoma* OR Chondromucosarcoma* OR fibrosarcoma* OR Dermatofibrosarcoma* OR "bednar tumor" OR "bednar tumour" OR "bednar's tumour" OR "bednar's tumor" OR Fibroblastoma* OR "Darrier ferrand" OR "darier ferrand" OR "darier hoffmann" OR Endotheliosarcoma* OR Neurofibrosarcoma* OR Haemangioendothelioma* OR Hemangioendothelioma* OR Hemangiosarcoma* OR "Heart muscle tumor" OR "heart muscle tumour" OR "Heart muscle tumors" OR "heart muscle tumours" OR

Haemangiosarcoma* OR Hemangiosarcoma* OR Histiosarcoma* OR histiocytoma* OR kaposi* OR Leiomyosarcoma* OR Liposarcoma* OR lymphangiosarcoma* OR "malignant peripheral nerve sheath tumour" OR "malignant peripheral nerve sheath tumor" OR "malignant peripheral nerve sheath tumours" OR "malignant peripheral nerve sheath tumors" OR mpnst OR Lymphangioendothelioma* OR "Mesodermal mixed tumor" OR "Mesodermal mixed tumour" OR "Mesodermal mixed tumors" OR "Mesodermal mixed tumours" OR Myosarcoma* OR "Myocardial tumor" OR "Myocardial tumour" OR "Myocardial tumors" OR "Myocardium tumor" OR "Myocardium tumour" OR "Myocardium tumors" OR "Myocardium tumours" OR Rhabdomyosarcoma* OR Myxosarcoma* OR Neurofibrosarcoma* OR Osteosarcoma* OR Cystosarcoma* OR Phyllodes OR "Rhabdoid tumor" OR "Rhabdoid tumour" OR "Rhabdoid tumors" "Rhabdoid tumours" OR "Small round cell tumor" OR "Small round cell tumour" OR "Small round cell tumors" OR "Small round cell tumours" OR Synovioma* OR Synoviasarcoma* OR Synoviosarcoma* OR "Muscle neoplasm" OR "Muscle neoplasms" OR "Muscle cancer" OR "Muscle cancers" OR "Vascular neoplasm" OR "Vascular neoplasms" OR "vascular cancer" OR "vascular cancers") 3660
#5 #1 OR #2 OR #3 OR #4 5124
#6 MeSH descriptor: [Hyperthermia, Induced] explode all trees 1556
#7 (oncotherm* or ehy-2000 or ehy-2030 or ehy-3010 or meht or "modulated electro-hyperthermia") 126
#8 #6 OR #7 1680
#9 #5 AND #8 with Cochrane Library publication date Between Jan 1990 and Dec 2019, in Trials 24

Database: clinicaltrials.gov
Search date: 2019-04-15
Hyperthermia AND sarcoma: 50
Thermotherapy AND sarcoma: 5

Database: clinicaltrials.gov
Search date: 2019-09-05
Oncothermia : 6

Database: WHO ICTRP
Search date: 2019-04-15
Hyperthermia AND sarcoma: 8
Thermotherapy AND sarcoma: 0

Database:WHO ICTRP
Search date: 2019-09-05
Oncothermia : 8

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A1: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence
ESMO-EURACAN Clinical Practice Guidelines	2018	Europe, USA, UK	**Local/locoregional disease**	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence
			The standard surgical procedure is a wide excision with negative margins (no tumour at the margin, R0). This implies removing the tumour with a rim of normal tissue around it	[II, A]
			marginal excision can be acceptable in carefully selected cases, in particular for extracompartmental atypical lipomatous tumours	[IV, B]
			wide excision is followed by radiotherapy (RT) as the standard treatment of high-grade (G2–3), deep, >5 cm lesions	[II, B]
			RT is not given in the case of a currently unusual, truly compartmental resection of a tumour entirely contained within the compartment	[IV, A]
			high-grade, deep,<5 cmlesions are also treated with surgery, followed by RT	[IV, A]
			RT is added in selected cases in the case of low- or high-grade, superficial, >5 cm and low-grade, deep, <5 cm STSs	[II, B]
			Reoperation in reference centres must be considered in the case of R1 resections (microscopic tumour at the margin), if adequate margins can be achieved without major morbidity, taking into account tumour extent and tumour biology (e.g. re-excision can be spared in extracompartmental atypical lipomatous tumours)	[IV, A]
			Mutilating surgery may be of choice in some cases. Options for limb-preserving surgery can be discussed with the patient, including ChT and/or RT or isolated hyperthermic limb perfusion with tumour necrosis factor alpha (TNF-a) plus melphalan	[III, A]
			if the tumour is confined to an extremity, or regional hyperthermia combined with ChT	[I, B]
			if the tumour is confined to an extremity, or regional hyperthermia combined with ChT	[I, B]
			There is no consensus on the current role of adjuvant ChT. Given the conflicting results of trials included in the meta-analyses, adjuvant ChT is not standard treatment in adult-type STS. It can be proposed as an option to the high-risk individual patient (high-grade, deep, >5 cm tumour) for a shared decision making with the patient	[II, C]

ESMO-EURACAN Clinical Practice Guidelines	2018	Europe, USA, UK	**Local/locoregional disease**	
			neoadjuvant ChT with anthracyclines plus ifosfamide for at least three cycles can be viewed as an option in the high-risk individual patient, for shared decision making	[II, Ca]
			RT should not delay the start of ChT and can be used preoperatively. Evidence has been provided about its tolerability when combined with preoperative ChT with full-dose epirubicin plus ifosfamide	[III, B]
			In one large randomised phase III study (in patients with G2– 3, deep, >5 cm STSs), regional hyperthermia in addition to systemic ChT was associated with a local progression-free survival (PFS) and DFS advantage	[I, B]
ESMO-EURACAN Clinical Practice Guidelines	2018	Europe, USA, UK	**Advanced/metastatic**	
			Metachronous (disease-free interval _1 year), resectable lung metastases without extrapulmonary disease are managed with surgery as standard treatment, if complete excision of all lesions is feasible	[IV, B]
			ChT may be added to surgery as an option, taking into account the prognostic factors (a short previous recurrence-free interval and a high number of lesions are adverse factors, encouraging the addition of ChT), although there is a lack of formal evidence that this improves outcome	[IV, B]
			ChT is preferably given before surgery in order to assess tumour response and thusmodulate treatment. In cases where lungmetastases are synchronous, in the absence of extrapulmonary disease, standard treatment is ChT	[III, B]
			Extrapulmonary metastatic disease is treated with ChT as the standard treatment	[I, A]
			Standard ChT is based on anthracyclines as the first-line treatment	[I, A]
			multi-agent ChT with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly in subtypes sensitive to ifosfamide, when a tumour response is felt to be potentially advantageous and patient performance status is good	[I, B]
			Angiosarcoma is highly sensitive to taxanes, which can be a treatment option in this histological subtype.	[III, B]
			An alternative is gemcitabine, possibly in combination with docetaxel	[V, B]
			Doxorubicin plus dacarbazine is an option for multi-agent, first-line ChT of LMS, in which the activity of ifosfamide is far less convincing in available retrospective evidence, or of solitary fibrous tumours	[V, B]
			Imatinib is standard medical therapy for those rare patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating	[III, A]

			surgery or with metastases deserving medical therapy	
			In patients with symptomatic progressive disease, imatinib, if available, can be considered, as it can induce tumour stabilisation or shrinkage and alleviate morbidity	[IV, C]
			After failure of anthracycline-based ChT, or the impossibility to use it, the following criteria may apply, although high-level evidence is lacking: ifosfamide	[IV, C]
			Trabectedin is an option for second line and beyond and is approved for advanced previously treated STS.	[I, B]
			pazopanib given until progression to advanced, previously treated STS patients (excluding liposarcomas). Thus, it is an option in non-adipogenic STS	[I, B]
			eribulin for liposarcomas	[II, A]
			gemcitabine/docetaxel is more effective than gemcitabine alone as second-line ChT, with special reference to LMS and undifferentiated pleomorphic sarcoma	[II, C]
			Regorafenib should be considered as an option, if available, in doxorubicinpretreated advanced, non-adipogenic STS patients	[II, C]
			Mammalian target of rapamycin (mTOR) inhibitors in malignant perivascular epithelioid cell tumours (PEComas)	[IV, C]
			Sirolimus activity in epithelioid haemangioendothelioma	[IV, C]
			Crizotinib in inflammatory myofibroblastic tumour associated with anaplastic lymphoma kinase (ALK) translocations	[IV, C]
			Sunitinib and cediranib in alveolar soft part sarcoma, where the molecular target is as yet unclear	[IV, C]
			Sunitinib in solitary fibrous tumours, where the molecular target is as yet unclear	[IV, C]
ESMO-EURACAN Clinical Practice Guidelines	2018	Europe, USA, UK	**Retroperitoneal sarcomas**	
			The standard treatment of primary lesions is surgery, to be carried out by a surgeon with specific sarcoma expertise. Surgery should be aimed at achieving a one-specimen en bloc, macroscopically complete resection, minimising microscopically positive margins. This is best done by resecting the tumour en bloc with adherent structures, even if not overtly infiltrated	[III, A]
			Although no randomised trials of neoadjuvant therapy versus resection alone for RPS have been reported to date, neoadjuvant treatment, in the formof ChT, external beamradiotherapy (EBRT), regional hyperthermia or combinations, is safe in well-selected patients andmay be considered after careful review by a multidisciplinary sarcoma tumour board	[IV, C]
			In one large randomised phase III study (in patients with G2–3, deep, >5cmSTSs), regional hyperthermia in addition to systemic ChT was associated with a local PFS and DFS advantage	[I,B]

Table A1.

Levels of evidence

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity

II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

III Prospective cohort studies

IV Retrospective cohort studies or case–control studies

V Studies without control group, case reports, experts opinions

Grades of recommendation

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc), optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

Evidence tables of individual studies included for clinical effectiveness and safety

Table A2: Characteristics of randomised controlled studies

First author	**Issels**
Year of publication	2010 and 2018 papers
Clinical trial identification number	NCT00003052 EORTC trial
Sponsorship source and role of funder	Supported by the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and by research grants from the Deutsche Krebshilfe and Helmholtz Association, as well as the National Institutes of Health (grant No. NIH P01 CA42745). The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
City, country of patient recruitment	Nine centres in four countries (six centres in Germany, one in Norway, one in Austria, one in the USA).
Setting	Inpatient (author input)
Article language	English

Declaration of interest	2010 paper: Dr Issels, Dr Lindner and Dr Abdel-Rahman have received consulting fees from Medtherm. All other authors declared no conflicts of interest. 2018 paper: Dr Issels has received travel support and honoraria from Pyrexar, PharmaMar, Medtherm and Bayer. Dr Lindner has received research and travel support from Dr Sennewald Medizintechnik; travel support from PharmaMar; and honoraria from Novartis, Lilly, Eisai, EL Medconsult. Mr Abdel-Rahman has received travel support and honoraria from Pyrexar and Medtherm. No other conflicts are reported.
Contact with authors	Yes
Study design	RCT
Choice of analysis set	2010 paper: ITT for effectiveness data, per protocol for proportional hazards model stratified by tumour site, as treated (only those that started chemo) for safety data 2018 paper: The authors stated that the survival-type analyses presented were based on the intention-to-treat population, which includes all eligible patients in the study who started their allocated treatment. However, patients that withdrew or developed metastatic disease were not included in the final analysis.
Inclusion criteria	Patients 18-70y With adult type soft tissue sarcoma that was primary or recurrent. The tumour had to have an Intermediate or high grade (FNCLCC classification), a diameter of 5cm or more, deep to the fascia.
Exclusion criteria	Patients with a low grade tumour; patients with evidence of distant metastases.
Number patients at baseline	2010 paper: n=341 Chemotherapy/radiotherapy + hyperthermia=169; Chemotherapy/radiotherapy only=172 2018 paper: n=341 randomized, 10 withdrew consent (I=6, C=4), 2 excluded because of metastatic diseases (I=1, C=1) , n= 329 presented in baseline data (I=162, C=167).
Age at baseline	Median 52, range 18-70
Gender (n, % female) at baseline	2010 paper: n=152, 44,5% 2018 paper: n=147, 45%
Tumour site	2010 paper: Non-extremity n=192 (56%), extremity n=149 (44%) 2018 paper: Non-extremity n=186 (56%), extremity n=143 (43%)
Disease status	2010 paper: Primary n=162 (48%), Recurrent n=37 (11%), Prior surgery n=142 (41%) 2018 paper: Primary n=157 (48%), recurrent n=37 (11%), prior surgery n=135 (41%)
Tumour size at baseline	2010 paper: Median 11cm, range 5-40cm 2018 paper: 5-12cm 61%, >12cm 39%
Tumour grading at baseline	FNCLCC grading system 2010 paper: G2 n=161 (47%), G3 n=178 (52%) 2018 paper: G2 n=153 (47%), G3 n=176 (53%)
Tumour depth at baseline (overall for both groups)	Not stated. Author feedback: Deep to the fascia.
Sarcoma histological subtype	2010 paper: Liposarcoma n=61 (18%), Leiomyosacoma n=54 (16%), Synovial sarcoma n=45 (13%), Sarcoma not otherwise specified n=73 (21%), Other sarcoma n=77 (23%), Not soft tissue sarcoma n=7 (2%), Unreviewed sarcoma n=24 (7%) 2018 paper: Liposarcoma n= 60 (18%), leiomyosarcoma n=52 (16%), Synovial sarcoma n=43 (13%), sarcoma NOS n=68 (21%), other sarcoma n=76 (23%), not soft tissue sarcoma n=6 (2%), Unreviewed sarcoma n=24 (7%)

WHO performance status	2010 paper: Status 0 n=225 (66%), Status 1 n=101 (30%), Status 2 n=15 (4%) 2018 paper: Status0 n=218 (66%), status1 n=96 (29%), status2 n=15 (5%)	
TNM-stage	Not stated in papers, author feedback: T2 N 0 / 1 M0 .	
AJCC prognostic stage group	Not stated in papers, author feedback: III B	
General description of intervention	>neoadjuvant: 4 cycles of chemotherapy + regional hyperthermia > best local therapy (surgery and/or radiotherapy) > adjuvant chemotherapy + regional hyperthermia	
General description of comparator	Same procedure without regional hyperthermia	
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: 42°C Planned dosage: 60 min Planned sessions: 16 Achieved tumour temperature: Tmax=41.8°C (median) T90=39.2°C (median) Achieved dosage: U Achieved sessions: Range 0-16	
Detailed description of chemotherapy	Etoposide 125 mg/m^2, ifosfamide 1500 mg/m^2, doxorubicin 50 mg/m^2, every 3 weeks	
Detailed description of radiotherapy	Dose 50–60 Gy, with 1.8–2.0 Gy daily fractions, boost up to 66 Gy delivered 4–6 weeks after surgery.	
Detailed description of surgery	Aim to definitively resect tumours, within 4–6 weeks of induction therapy	
Description of any other concomitant treatments	None stated	
Outcome – Overall survival	**2010 paper** *Number of Deaths: I 44% vs C 46% *HR 0.88 (0.64–1.21) p 0.43 *Median duration: I=79 months (95% CI 54 to >120) vs C=73 months (95% CI 45 to >120) Overall survival defined as time from randomisation to death from any cause.	**2018 paper** *Number of Deaths: I 53,7% vs C 60,5%
Outcome – Disease specific survival		*Death by disease or treatment: I 47.5% vs C 58.1% *Survival rate at 5y: I 62.7% (95% CI, 55.2%-70.1%) vs C 51.3% (95% CI 43.7%-59.0%) *Survival rate at 10y: I 52.6% (95% CI, 44.7%-60.6%) vs C 42.7% (95% CI, 35.0%-50.4%) *NNT at 5 y: 8.8 *NNT at 10y: 10.1 *HR 0.73; 95% CI,0.54-0.98; P = .04 *Median duration: I=15.4 years (95% CI 6.6 to >17.0), C=6.2 years (95% CI 3.2–10.3) The survival benefit has been analyzed as death due to disease or its treatment
Outcome - Local progression-free survival	*Proportion at 2y: I=76% (70–83), C=61% (53–69) *Proportion at 4y: I=66% (58–74), C=55% (48–64) *HR: 0.58 (95% CI 0.41–0.83) p=.003 *Median duration progression free survival: 6.3 years in I and C	*Patients with local progression: not stated *HR: 0.65 (95% CI, 0.49-0.86; p= .002) *Median duration progression free survival: I=5.6 years (95% CI 2.9–8.7), C=2.4 years (95% CI 1.7–4.2)

	Defined as time from randomisation to confirmed local progression, relapse, or death, whichever occurred first and irrespective of any occurrence of distant metastases.	
Outcome-Disease-free survival	*Proportion at 2y: I=58% (51–66), C=44 (37–52) *Proportion at 4y: I=42% (35–51), C=35 (28–43) *HR 0.70 (0.54–0.92) p 0.011 *Median duration disease free survival: I=2.7 years vs C=1.5 years Defined as time from randomisation to confirmed local failure, distant metastases, or death due to disease or treatment, whichever occurred first.	*Patients with disease free survival: not stated *HR 0.71 (95% CI 0.55-0.93; P = .01) *Median duration disease free survival: I=2.8 years (95% CI 2.0–4.9), C=1.5 years (95% CI 1.1–2.1)
Outcome – objective response rate	I=28.8% vs C=12.7% Defined as sum of complete and partial response.	I=29.8% vs C=12.9%
Outcome-Amputation	I= 6.7% vs C=8.9% Denominator is patients that received definitive surgical resection	I=8.8% vs C=10.5% Denominator is patients that received definitive surgical resection
Outcome – adverse events	Adverse events related to chemotherapy (CTC criteria) Deaths due to treatment I=1.2% vs C=0.6% Haematological Acute Leukaemia I=1.8% vs C=1.2% Leucopenia grade 3-4 I=77.6% vs Cn=63.5% Thrombocytopenia grade 3-4 I=17.0% vs C=13.8% Non-haematological grade 3-4 Nausea I=13.9% vs C=15.6% Vomiting I=9.1% vs C=5.4% Nephrotoxicity I=1.2% vs C=1.2% Cardiotoxicity I=1.8% vs C=2.4% Neurotoxicity I=9.1% vs C=4.8% Fever of unknown origin I=0.6% vs C=3.0% - Complications related to hyperthermia: CTC v 1.0, *pain (Power related) : mild to moderate in 40,5% and severe in 4.3% *bolus pressure: mild to moderate in 26.4% and severe in 4.9% *skin burn: mild to moderate in 17.8% and severe in 0.6% *Tissue necrosis: mild to moderate in 4.3% and severe in 2.5% *Localised infection: mild to moderate in 3.1% and severe in 1.2% Others (claustrophobia, not Power related pain, wound healing disorder, nausea): mild to moderate in 14.1% and severe in 8.6%	*Death by treatment: I=3.1% vs C=1.2%
Outcomes – follow up duration	The total follow-up time was 128 months, the median follow up time was I=36 months, C=32 months.	The median (interquartile range) follow-up duration was 11.3 (9.2-14.7) years

	Follow-up forms were completed every 3 months during the first year, every 4 months for 2 years, every 6 months up to 5 years, and yearly thereafter.	
Withdrawals (patients who withdrew from the study after enrollment with reason)	None	I=3.6% (6/169 rand) C=2.3% (4/172 rand.)
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	No data available	
Random sequence generation	Use of block randomisation based on a computer generated list with stratification according to site (extremity vs non-extremity), presentation of tumour (primary vs recurrent vs prior surgery), and centre.	
Allocation concealment	Block randomisation was done centrally at the EORTC data centre. After informed consent by a suitable patient, the study centre reported relevant information to the EORTC data centre, and treatment allocation was communicated by fax to the study centre. Balanced baseline patient characteristics.	
Blinding of participants and personnel	Participants and personnel were not blinded for the allocated treatment. There is a difference in the number of patients that received post-induction chemotherapy. The authors state that this is driven by the effect of the induction therapy because progress or death during induction therapy implies no post-induction chemotherapy.	
Blinding of outcome assessment	Overall survival and amputation are objective outcomes. Adverse events were objective outcomes that were graded according to CTCAE. Local progression-free survival, disease-free survival and objective response rate are subjective outcomes. Responses (complete response and partial response) have been confirmed by external review (independent review committee) in 48 of 50 patients. Classifications for stable disease, progressive disease, could not be evaluated were not verified by the committee and misclassifications could have occurred.	
Incomplete outcome data	Objective response rate: n=97 patients had no measurable disease at the start and were not evaluated in this analysis. Response to induction therapy could not be evaluated in n=21 Amputation: 4 missing data about surgery in control group for Issels 2010.	
Selective reporting	2010 paper: Relapse free survival was stated as a secondary outcome in the clinicaltrials.gov protocol, but not reported. The 2015 Datecan guidelines for time-to-event end point definitions in sarcomas in Cancer trials considers relapse-free survival as an irrelevant/ambiguous end point. The full trial protocol also mentionned time to progression. The result of definitive surgery was not stated in the clinicaltrials.gov protocol, but this was mentioned in the full trial protocol. 2018 paper: While the trial protocols planned to evaluate overall survival, this paper reports on disease-specific survival. The authors explain that "owing to the fact that our study comprises a 20-year data set that included an older age group between 41 to 70 years that represented more than 70% of the patients, there was an increasing risk of death from natural causes unrelated to sarcoma. Therefore, the survival benefit has been analyzed as death due to disease or its treatment so to be not confounded by the occurrence of disease-unrelated deaths."	
Other sources of bias	Two authors received travel support and honoraria from Pyrexar which is the manufacturer of the device that was evaluated.	

Table A3: Characteristics of included single arm studies

First author	**Baur**
Year of publication	2003
Clinical trial identification number	Not stated

Sponsorship source and role of funder	Supported by 'Deutsche Krebshilfe'.
City, Country of patient recruitment	Munich, Germany
Setting	6-8 days hospitalisation for each cycle of chemotherapy and hyperthermia
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated
Inclusion criteria	High grade STS of musculoskeletal system, primary or recurrent
Exclusion criteria	Intraperitoneal or retroperitoneal sarcomas
Number patients at baseline	n=19
Age at baseline	Mean 51y, range 24–72y
Gender (n, % female) at baseline	n=9, 47%
Tumour site at baseline	Extremity n=14 (74%), trunk n=3 (16%), axilla n=1 (5%), neck n=1 (5%)
Disease status at baseline	Primary or recurrent tumours, no numbers given No patient had metastatic disease prior to therapy
Tumour size at baseline	1668cm^3, range 217-4640cm^3
Tumour grading at baseline	G2 n=10, G3 n=9
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Primitive neuroectodermal tumour n=2 (11%), chondrosarcoma n=2 (11%), malignant fibrous histiocytoma n=4 (21%), leiomyosarcoma n=1 (5%), liposarcoma n=3 (16%), spindle cell sarcoma n=2 (11%), synovial sarcoma n=2 (11%), rhabdomyosarcoma n=1 (5%), unclassified sarcoma n=1 (5%), malignant schwannoma n=1 (5%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Neoadjuvant chemotherapy + regional hyperthermia
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: Tmax ≥42°C Planned dosage: 60 min (30 min preheating) Planned sessions: 8 Achieved tumour temperature: Tmax=42.5°C (mean) T90=38.9°C (mean) Achieved dosage: U Achieved sessions: U
Detailed description of chemotherapy	4 courses of doxorubicin 50 mg/m^2 (day 1), etoposide 125 mg/m^2 (days 1+4) and ifosfamide 1500 mg/m^2 (days 1–4)
Detailed description of radiotherapy	None
Detailed description of surgery	not described
Description of any other concomitant treatments	Not stated
Adverse events	Intratumoural bleeding no=11 G1-2=7, G3-4=1 Oedema in surrounding soft tissue no=8 G1-2=10, G3-4=1 Muscle necrosis n=0 Bone marrow necrosis n=0 Infection (planned outcome but not reported)

	The data were graded (where possible) according to CTCAE with input from clinical experts.
Follow-up period	mean 34 months
Withdrawals (patients who withdrew from the study after enrollment with reason)	No withdrawals
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants, data from 19 consecutive patients 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: No indications of any deviations 5.Bias due to missing data: Data were complete 6.Bias in measurement of outcomes: Objective outcomes, less explicit grading system 7.Bias in selection of the reported result: No protocol information available, reporting about infection was planned, but not reported upon

First author	**Fiegl**
Year of publication	2004
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Not stated
City, Country of patient recruitment	Munich, Germany
Setting	Not stated
Article language	English
Declaration of interest	No author has any financial or personal relationship with other people or organizations that could have influenced this work.
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated. For a sub-fraction of patients with local bulky disease, where hyperthermia was technically feasible, the ICE regimen was also combined with RHT.
Inclusion criteria	>16y; histologically confirmed locally advanced soft tissue sarcoma with or without metastases; ECOG performance status of 1 or less; should not display any severe organ (heart, liver and kidney) dysfunction. As pretreatment, chemotherapy including doxorubicin plus ifosfamide with or without etoposide were allowed. Patients were required to show progressive disease (PD) to the previous regimen at the time to be considered for second line study treatment.
Exclusion criteria	Ewing's sarcoma, osteosarcoma and malignant gastrointestinal stromal tumours (GIST) were excluded.
Number patients at baseline	n=20, subfraction that received hyperthermia n=13
Age at baseline	Median 50y, range 17–62y
Gender (n, % female) at baseline	n=9, 45%
Tumour site at baseline	Trunk n=8 (40%), abdomen n=8 (40%), pelvis n=4 (20%)
Disease status at baseline	100% pretreated locally advanced n=8 (40%), metastic n=12 (60%)
Tumour size at baseline	Not stated
Tumour grading at baseline	Grading system not stated G2 n=7 35% G3 n=13 65%
Tumour depth at baseline	Not stated

Sarcoma histological subtype	Liposarcoma n=4 (20%), Leiomyosarcoma n=5 (25%), Malignant fibrous histiocytoma n=2 (10%), Schwannoma n=1 (5%), Rhabdomyosarcoma n=1 (5%), Fibrosarcoma n=1 (5%), Undifferentiated sarcoma n=3 (15%), Other n=3 (15%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Chemotherapy + regional hyperthermia (for a subfraction of patients). Note: Judged by the clinical experts as neoadjuvant.
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: Tmax = 42°C Planned dosage: 60 min Planned sessions: U Achieved tumour temperature: Tmax=41°C (mean) Achieved dosage: U Achieved sessions: U
Detailed description of chemotherapy	ifosfamide 1.5 g/m^2, carboplatin 100 mg/m^2 and etoposide 150 mg/m^2 Each cycle repeated after 4 weeks
Detailed description of radiotherapy	Nothing stated
Detailed description of surgery	Nothing stated
Description of any other concomitant treatments	Granulocyte-colony stimulating factor (G-CSF) 5 mg/kg
Adverse events	Toxicity was evaluated after each treatment cycle according to CTC Maximal toxicity of chemotherapy (expressed as number of patients) Leukopenia G1 n=6, G2 n=3, G3 n=3, G4 n=8 Thrombopenia G1 n=8, G2 n=2 G3, n=6, G4 n=4 Nausea/vomitting G1 n=5, G2 n=4, G3 n=1, G4 n=0 Alopecia G2 n=20 Infections G1 n=2, G2 n=5, G3 n=2, G4 n=0 Renal G1 n=4, G2 n=1, G3 n=0, G4 n=0 Neurology G1 n=1, G2 n=0, G3 n=0, G4 n=0 Gastrointestinal G1 n=0, G2 n=0, G3 n=1, G4 n=0 Among 13 patients receiving hyperthermia Mild to moderate AE= pain within the applicator and mild erythema. Severe to life-threatening AE= 0 patients
Follow-up period	Median of 15 months.
Withdrawals (patients who withdrew from the study after enrollment with reason)	No withdrawals
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from intended intervention, but these reflect usual practice 5.Bias due to missing data: Data were complete, 20 patients enrolled and adverse events reported for all 6.Bias in measurement of outcomes: Objective outcomes and use of an explicit grading system 7.Bias in selection of the reported result: No protocol information available

First author	**Hayashi**
Year of publication	2015

Clinical trial identification number	UMIN000013056
Sponsorship source and role of funder	Not stated
City, Country of patient recruitment	Kanazawa, Japan
Setting	Trial registry mentions inpatient as inclusion criteria
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated
Inclusion criteria	Patients with soft tissue sarcoma that had previous unplanned excision with smaller surgical margins than usual for soft tissue sarcoma.
Exclusion criteria	Patients with low grade sarcomas; tumours in pelvic and dorsal regions; age <15 or ≥70 years , performance status of >2, white blood cell count <3000/μl, neutrophil count <1500/μl, platelet count <75000/μl, hemoglobin <7g/μl, creatinine clearance <60 ml/min, aspartate aminotransferase/alanine aminotransferase >75 IU/l (male) or 67.5 IU/l (female), total bilirubin >3.0 mg/dl, left ventricular ejection fraction <50%, no documented consent obtained, and allergies to any of the drugs used in the study
Number patients at baseline	n=6
Age at baseline	Mean 54y, range 39-66y
Gender (n, % female) at baseline	n=3, 50%
Tumour site at baseline	Extremity n=6 (100%)
Disease status at baseline	100% prior surgery
Tumour size at baseline	Not stated
Tumour grading at baseline	FNCLCC, Grade III n=6, 100%
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Malignant fibrous histiocytoma n=3 (50%), myxoid liposarcoma n=1 (17%) , sclerosing epithelioid fibrosarcoma n=1 (17%), and synovial sarcoma n=1 (17%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Trimodal therapy including radiotherapy, hyperthermia and chemotherapy before second look surgery. 5/6 patients also got postoperative chemotherapy which was not described in the planned treatment protocol. Note: judged by clinical experts as adjuvant treatment.
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: Thermotron RF-8 Target tumour temperature: >42,5°C Planned dosage: 60 min Planned sessions: 5 Achieved tumour temperature: U Achieved dosage: U Achieved sessions: 4-5
Detailed description of chemotherapy	cisplatin (100 mg/m^2), pinorubin (an adriamycin derivative; 30 mg/m^2) and ifosfamide, 5 sessions + 1 systemic session
Detailed description of radiotherapy	dose of 2 Gy, five days per week, over 16 sessions, for a total dose of 32 Gy
Detailed description of surgery	surgery performed after triple modality treatment
Description of any other concomitant treatments	Not stated
Adverse events	CTCAE v3.0

	-Any adverse events: 29 AEs occurred among 6 patients (mean of 4,8 AE per patient) -Death by AE= 0/6 0% (95% CI 0-46%) died within the average follow-up period of 10,9y (range 8,1-17,6y) AE related to preoperative radiotherapy-chemotherapy-hyperthermia (Data presented as number of patients with adverse event): Anemia n=6 G2=5 G3=1 Neutropenia n=6 G2=1 G3=2 G4=3 Thrombocytopenia n=4 G2=2 G3=2 Vomiting n=3 G1=2 G2=1 Wound complication n=3 G1=1 G2=2 Burn n=3 G1=1 G2=2 Vasculitis n=1 G2=1 Creatinine n=1 G1=1 Rectal hemorrhage n=1 G2=1 Edema, limbs n=1 G1=2 (potential error in the table 2 in the paper) No stratified data for early/late toxicity
Follow-up period	Average of 10,9y (range 8,1-17,6y)
Withdrawals (patients who withdrew from the study after enrollment with reason)	No withdrawals
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: Data were complete, six patients enrolled and complete data available 6.Bias in measurement of outcomes: Objective outcomes and use of an explicit grading system 7.Bias in selection of the reported result: Published protocol that states that adverse events would be recorded

First author	**Issels**
Year of publication	2001
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Supported by the Deutsche Krebshilfe and the European Society of Hyperthermic Oncology (ESHO).
City, Country of patient recruitment	Munich, Germany
Setting	Patients were hospitalised during the thermochemotherapy cycles for an average time of 8 days
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated.
Inclusion criteria	Histologically-confirmed soft tissue sarcoma without evidence of distant disease only progressively growing tumours of grade II or III, tumour size >8 cm and extracompartmental extension were eligible. Patients were required to have Karnofsky performance status of >=60%, normal haematological, renal and hepatic function. Patients with persistent or recurrent high-risk STS after previous attempts of resection with or without radiotherapy were eligible.

Exclusion criteria	Not stated
Number patients at baseline	n=59
Age at baseline	Mean 50y, range 21–77y
Gender (n, % female) at baseline	n=28 (47%)
Tumour site at baseline	Trunk n=8 (14%), abdomen n=5 (8%), pelvis n=18 (31%), extremity tumours n=28 (47%)
Disease status at baseline	Primary n=31 (53%), Local recurrence n=28 (47%), Prior surgery n=38 (64%)
Tumour size at baseline	Median ellipsoidal tumour volume 300 cc 71% of the primary tumour diameters >=8cm
Tumour grading at baseline	G2 n=28 (48%), G3 n=31 (52%)
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Liposarcoma n=14 (24%), Malignant fibrous histiocytoma n=13 (22%), Leiomyosarcoma n=10 (17%), Schwannoma n=6 (10%), Synovial sarcoma n=3 (5%), Rhabdomyosarcoma n=3 (5%), Extraskeletal Ewing's sarcoma n=2 (3%), Undifferentiated sarcoma n=4 (7%), Others n=4 (7%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	>Neoadjuvant chemotherapy + regional hyperthermia >Surgery >Adjuvant chemotherapy + regional hyperthermia + radiotherapy (for non-preradiated patients)
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: Tmax ≥42°C Planned dosage: 60 min Planned sessions: 16 Achieved tumour temperature: Tmax=42,5°C (mean) T90=39,8°C (mean) Achieved dosage: U Achieved sessions: preoperatively 8 (median), range 4–10 postoperatively 5 (median), range 2-8
Detailed description of chemotherapy	Neoadjuvant chemotherapy: 4 courses (every 3 weeks) of doxorubicin (adriamycin) 50 mg/m^2, etoposide 125 mg/m^2, and ifosfamide 1250 mg/m^2 Adjuvant chemotherapy: 4 cycles of etoposide (150 mg/m^2 on day 1–5) and ifosfamide (1500 mg/m^2 on days 1–5), every 4weeks
Detailed description of radiotherapy	Non-pre-irradiated patients with positive surgical margins or residual macroscopic disease were selected for external beam radiotherapy using mega-voltage equipment.External beam radiotherapy using mega-voltage equipment, total doses (range 55–65 Gy) in daily fractions (1.8–2.0 Gy)
Detailed description of surgery	Surgery for those judged to be resectable
Description of any other concomitant treatments	Not stated
Adverse events	WHO scale, toxicity during neoadjuvant chemotherapy + regional hyperthermia Expressed as the percentage of patients experiencing each grade of toxicity. Leucopenia G1 n=1 2% G2 n=8 13%G3 n=36 61% G4 n=13 22% Thrombocytopenia G1=48% G2=2% G3=8% G4=0% Nausea/vomiting G1=39% G2=42% G3=2% G4=0% Alopecia G1=10% G2=34% G3=56% G4=0% Infection G1=20% G2=4% G3=8% G4=2% Renal toxicity G1=2% G2=0% G3=0% G4=2% Neurotoxicity G1=15% G2=17% G3=2% G4=2% Cardiac toxicity G1=13% G2=12% G3=0% G4=0%

	Pain within the applicator G1=8% G2=66% G3=14% G4=0% Skin burn G1=0% G2=7% G3=12% G4=0% Fever G1=12% G2=24% G3=0% G4=0% No specifications about toxicity for adjuvant treatment
Follow-up period	Median follow-up 85 months
Withdrawals (patients who withdrew from the study after enrollment with reason)	Neoadjuvant therapy stopped because of toxicity or refusal in 6 patients. Adjuvant therapy stopped because of toxicity in 1 patient and refusal in 3 patients. Among the 20 patients who did not receive the postoperative protocol treatment, 9 refused further treatment.
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: Adverse events data available for all the patients 6.Bias in measurement of outcomes: Objective outcomes and use of an explicit grading system 7.Bias in selection of the reported result: No protocol information available

First author	**Maguire**
Year of publication	2001
Clinical trial identification number	Not stated
Sponsorship source and role of funder	This work was supported by NIH/NCI grant #CA 42745.
City, Country of patient recruitment	Durham, US
Setting	Not stated
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Per protocol. Only those patients with heatable tumours were evaluated for treatment-induced toxicity.
Inclusion criteria	Patients 18 years and more with Karnofsky performance status 70% and more and life expectancy >6 months were enrolled. All patients had histologically proven grade 2 or 3, deep, undisturbed soft tissue sarcomas that were accessible for invasive thermometry.
Exclusion criteria	Pregnant patients and those with cardiac pacemakers or implanted defibrillators were not eligible.
Number patients at baseline	n=35
Age at baseline	Median 58y, range 20-83y
Gender (n, % female) at baseline	n=14, 40%
Tumour site at baseline	Extremity n=29 (83%), trunk n=6 (17%)
Disease status at baseline	Not stated
Tumour size at baseline	5-10cm n=19 (54%), >10 n=16 (46%)
Tumour grading at baseline	II n=8 (23%), III n=23 (66%), high grade, unspecified n=4 (11%)

Tumour depth at baseline	Not stated
Sarcoma histological sub-type	Not stated
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Neoadjuvant radiotherapy combined with hyperthermia followed by surgery
General description of comparator	Not applicable
Detailed description of hyperthermia	All patients received a 1h test Hyperthermia to assess if the tumour was heatable. Five out of 35 patients (14%) had tumours that were ultimately classified as not heatable. Hyperthermia Device: BSD-2000 Target tumour temperature: Tmax=55°C Planned dosage: 60-120minCEM 43°C T90 of 10-100 Planned sessions: Max 10 Achieved tumour temperature: U Achieved dosage: CEM 43°C T90=90 min (mean) 38 min (median), range 0.1-601 min At thermal goal of CEM 43°C T90 ≥ 10 n=25 Achieved sessions: U
Detailed description of chemotherapy	None
Detailed description of radiotherapy	All patients were treated with megavoltage (>= 4 MV) external beam radiation at SSD/SAD >=80 cm, 50 Gy in 5 weeks, 1.8± 2 cGy/fraction.
Detailed description of surgery	4-6 week after thermoradiotherapy, Limb-sparing surgery (LSS) with wide margins was the goal for all patients with extremity lesions, whilst wide local excision (WLE) was the goal for patients with truncal tumours.
Description of any other concomitant treatments	Not stated
Adverse events	Any acute adverse events (per protocol): *10/30 patients (33%, 95% CI 17-53%) experienced acute adverse events *12 adverse events among 30 patients (mean of 40 AE per 100 patients) Mild to moderate acute AE (per protocol): * 5 mild to moderate acute adverse events occurred among 30 patients (mean of 17 mild to moderate acute AE per 100 patients) Severe to life-threatening acute AE (per protocol): *7 severe to life-threatening acute adverse events occurred among 30 patients (mean of 23 severe to life-threatening acute AE per 100 patients) Severe to life-threatening late AE: *0/30 patients (0%, 95% CI 0-11%) experienced severe to life-threatening late adverse events Burns G1-2 n= 3, G3-4 n= 2 Wound infections G3-4 n=4 Severe oedema G3-4 n=1 Catheter infection G1-2 n=1 Fat necrosis G1-2 n=1 The data were graded according to CTCAE with input from clinical experts. Authors state that there was no correlation found between thermal dose and development of treatment-induced toxicity. Data was not shown.
Follow-up period	Not clear
Withdrawals	Two patients elected to discontinue radiotherapy after 30 Gy.
Any data on patient satisfaction, shared decision	Not stated

making measures, procedural time or resource use	
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: Only those patients with heatable tumours were evaluated for treatment-induced toxicity. 6.Bias in measurement of outcomes: Objective outcomes, no grading 7.Bias in selection of the reported result: No protocol information available
Any other comments	It is possible that Maguire 2001 and Prosnitz 1999 both included the soft tissue sarcoma patients that were treated in the period 1994-1996. The size of this overlap is unclear.

First author	**Makihata**
Year of publication	1997
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Grant-in-Aid for Cancer Research (6-23) from the Ministry of Health and Welfare
City, Country of patient recruitment	Okayama, Japan
Setting	Not stated
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated
Inclusion criteria	Patients with soft tissue sarcoma
Exclusion criteria	Not stated
Number patients at baseline	n=14
Age at baseline	Mean 53y, range 19-78y
Gender (n, % female) at baseline	n=7, 50%
Tumour site at baseline	Extremity n= 13 (93%), trunk n=1 (7%)
Disease status at baseline	Not stated
Tumour size at baseline	Tumour volume mean 251cm^3, range 11-1716cm^3
Tumour grading at baseline	Not stated
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Malignant fibrous histiocytoma n=6 (43%), synovial sarcoma n=3 (21%), Ewing's sarcoma n=1 (7%), Clear cell sarcoma n=1 (7%), Liposarcoma n=1 (7%), Epitheloid sarcoma n=1 (7%), Unclassified sarcoma n=1 (7%)
WHO performance status	Not stated
TNM-stage	Stage III n=11, Stage IIB n=2, Stage IB n=1
AJCC prognostic stage group	Not stated
General description of intervention	>Neoadjuvant thermo-radio-chemotherapy in 11 cases, and thermo-radiotherapy or thermo-chemotherapy in 3 other cases >Surgery
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-1000/ HEH-500C Target tumour temperature: >42°C Planned dosage: 60 min

	Planned sessions: U Achieved tumour temperature: Tmax=43,4°C (mean),range 39.2-50.2°C Taverage=42,2°C (mean), range 38,9-47,8°C Achieved dosage: Time ≥ 42°C= 280,6min, range 0-471min Achieved sessions: 8 (mean), range 4-14
Detailed description of chemotherapy	MAID regimen (2-mercaptoethanesulphonic acid (mesna) 900mg/m^2, adriamycin 15mg/m^2, ifosfamide 1,5g/m^2 and dacarbazine 200mg/m^2). Some patients received vincristine, cis-platinum and/or carboplatin.
Detailed description of radiotherapy	4-5 x/week, dose 1.8 2Gy/fraction, total of 30-40Gy in a 4w period. Radiotherapy with Mavatoron-77 device which administered 6MV x-ray and 6MeV electron
Detailed description of surgery	Surgical resection of tumours after completion of preoperative treatment (mean 22d, range 9-41d after completion) Amputation n=1, wide resection n=13
Description of any other concomitant treatments	Not stated
Adverse events	Including results from hyperthermia and surgery, not clear if there were any adverse events from radiotherapy or chemotherapy Any adverse event: *14 adverse events among 14 patients (mean of 1 AE per patient) Mild to moderate AE * There were 8/14 patients (57%, 95% CI 29-82%) patients with mild to moderate AE. as maximum toxicity Severe to life-threatening AE *There were 2/14 (14%, 95% CI 2-43%) patients with severe to life-threatening AE. Amputation due to AE *1/14 patients with amputation due to wound infection. Burns G1-2 n=8 Delayed healing G1-2 n=2 Wound infection G3-4 n=2 Hematoma G1-2 n=2 The data were graded according to CTCAE with input from clinical experts.
Follow-up period	Mean follow up 27 months, range 8-61 months
Withdrawals (patients who withdrew from the study after enrollment with reason)	Not stated
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: Data were complete 6.Bias in measurement of outcomes: Objective outcomes, no grading 7.Bias in selection of the reported result: No protocol information available

First author	**Prosnitz**
Year of publication	1999
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Supported in part by NIH/NCI Grant CA 42745

City, Country of patient recruitment	Durham, US
Setting	Not stated
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Intention to treat. The authors stated that no further hyperthermia was given to unheatable patients, but they were included in the clinical data analysis.
Inclusion criteria	>18y Grade 2 or 3 STS no distant metastases who were candidates for surgical resection
Exclusion criteria	Excluding rhabdomyosarcoma; Patients with an excisional biopsy performed were excluded as were those with a subtotal excision of tumour rendering them technically unsuitable for hyperthermia; Patients with localized but unresectable disease were also excluded.
Number patients at baseline	n=97
Age at baseline	Median 54y, range 6-89
Gender (n, % female) at baseline	n=39, 40%
Tumour site at baseline	Extremity n=78 (80%), pelvis n=6 (6%), trunk n=12 (12%), retroperitoneum n=1 (1%)
Disease status at baseline	Not stated
Tumour size at baseline	=< 5cm n=10 >5cm =<10cm n=43 >10cm n=44
Tumour grading at baseline	Not stated
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Malignant fibrous histiocytoma n=42 (43%), Liposarcoma n=23 (24%), undifferentiated n=6 (6%), synovial cell n=8 (8%), sarcoma not otherwise specifed n=4 (4%), fibrosarcoma n=3 (3%), malignant primitive nerve tumour n=3 (3%), neurofibrosarcoma n=4 (4%), leiomyosarcoma n=1 (1%), alveolar soft part n=1 (1%), epithelioid n=1(1%), angiosarcoma n=1 (1%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Neoadjuvant radiotherapy + hyperthermia, surgery, (unplanned adjuvant chemotherapy for some patients)
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: 42,5°C Planned dosage: 60min after reaching 42.5°C CEM 43°C T90 of 10-100 Planned sessions: U Achieved tumour temperature: U Achieved dosage: CEM 43° T90=32 min (extremities), 9min (non-extremities), 43min (2 sessions/week) protocol), 14 min (1 session/week) (medians) Achieved sessions: U
Detailed description of chemotherapy	Adjuvant chemotherapy was not part of the protocol therapy. However 8 patients did receive it
Detailed description of radiotherapy	megavoltage equipment, 4–6 MV, dose of 5000–5040 cGy at 180–200 cGy/fraction
Detailed description of surgery	4 -6 weeks following radiation and hyperthermia. The intent was to achieve a wide surgical margin circumferentially.
Description of any other concomitant treatments	Not stated
Adverse events	*38/97 patients (39%, 95% CI 29-50%) experienced adverse events *57 AEs occurred among 38 patients (mean of 1,5 AE per patient)

	*3/97 patients (3% 95% CI 1-9%) died because of AE. Three additional deaths because of unclear reasons for which the authors assumed that they were related to the sarcoma. *4 amputations (4% 95% CI 1-10%) due to complications. Combined treatment related (expressed as number of complications) Wound infection n=23 Extremity edema n=7 Vascular injury n=3 Peripheral neuropathy n=3 Fracture n=2 Frozen shoulder n=1 Hyperthermia related Second-degree burn n=9 Third-degree burn n=2 Fat necrosis n=2 Catheter complications n=2 Chemotherapy-related Cardiomyopathy n=1
Follow-up period	median 32, range 12 -155 months
Withdrawals (patients who withdrew from the study after enrollment with reason)	None stated
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: Changes mid-way in the protocol and there were deviations from intended intervention, but these reflect usual practice 5.Bias due to missing data: Not clear if there were missing data 6.Bias in measurement of outcomes: Objective outcomes, no grading Quote "In an additional three patients, the exact cause of death was not known but was likely related to their sarcoma and was scored as such." 7.Bias in selection of the reported result: No protocol information available
Any other comments	It is possible that Maguire 2001 and Prosnitz 1999 both included the soft tissue sarcoma patients that were treated in the period 1994-1996. The size of this overlap is unclear.

First author	**Uno**
Year of publication	1995
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Not stated
City, Country of patient recruitment	Tokyo, Japan
Setting	Not stated
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated
Inclusion criteria	Patients with histologically confirmed soft tissue sarcoma
Exclusion criteria	Not stated

Number patients at baseline	n=8
Age at baseline	Mean 49y, range 17-78y
Gender (n, % female) at baseline	n=5, 63%
Tumour site at baseline	Extremity n=1 (12,5%), trunk n=5 (62,5%), abdominal n=1 (12,5%), head and neck n=1 (12,5%)
Disease status at baseline	Prior surgery n=5, prior chemotherapy n=3
Tumour size at baseline	Mean 86 cm^2, range 24-260 cm^2
Tumour grading at baseline	G1=1, G2=2, G3=5
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Synovial sarcoma n=1 (12,5%), angiosarcoma n=1 (12,5%), malignant fibrous histiocytoma n=3 (37,5%) (One of the patients with MFH is likely to be a bone sarcoma), leiomyosarcoma n=1 (12,5%), chondrosarcoma n=1 (12,5%), neurofibrosarcoma n=1 (12,5%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Trimodal therapy including chemotherapy, radiotherapy and hyperthermia
General description of comparator	Not applicable
Detailed description of hyperthermia	THyperthermia Device: Thermotron RF-8 Target tumour temperature: U Planned dosage 45-60min Planned sessions: 3-6 Achieved tumour temperature: Tmax=range 41,1-43,0°C Taverage=range 40,0-42,4°C Achieved dosage: U Achieved sessions: 3-6
Detailed description of chemotherapy	At least two courses of doxorubicin 12mg/m^2/d for 5 days
Detailed description of radiotherapy	Conventional fractionation with x-rays and/or electron beams, 9-10Gy/week, mean dose 61.9 Gy for 7 patients, 1 patient with 41,6Gy
Detailed description of surgery	Nothing stated
Description of any other concomitant treatments	Not stated
Adverse events	-Patients with mild to moderate AE: All patients 8/8 100% (95% CI 63-100%) experienced a mild to moderate acute AE -Patients with severe to life-threatening AE: All patients 8/8 100% (95% CI 63-100%) experienced a severe to life-threatening acute AE. -Patients had on average 1,8 acute severe to life-threatening AE and 1,9 acute mild to moderate AE Acute toxicities (expressed as patients with AE) Skin reactions: G1-2 n=4, G3-4 n=4 Pharyngeal mucositis G3-4 n=1 Leukopenia G1-2 n=1, G3-4 n=7 platelets G1-2 n=2 Radiatation pneumonitis G3- 4 n=2 Alopecia G1-2 n=8 Some data were graded according to CTCAE with input from clinical experts.
Follow-up period	mean 20 months, range 7-39months
Withdrawals (patients who withdrew from the study after enrollment with reason)	Nothing stated

Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: Adverse events reported for all enrolled patients 6.Bias in measurement of outcomes: Objective outcomes and use of an explicit grading system 7.Bias in selection of the reported result: No protocol information available

First author	**Volovat**
Year of publication	2014
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Not stated
City, Country of patient recruitment	Iasi, Romania (assumed, not stated)
Setting	Not stated
Article language	English
Declaration of interest	Not stated
Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated, the paper reports data for 18 patients out of 24 that were enrolled
Inclusion criteria	Patients diagnosed with metastatic soft tissue sarcoma and progressive disease after doxorubicin treatment. Every patient received minimum 2 cycles of doxorubicin before progression of the disease. A minimum of 2 points at ECOG performance status evaluation, no major cardiac disease, adequate bone marrow, good hepatic and renal functions, retroperitoneal or abdominal soft tissue sarcoma with positive histopathology and no c-KIT mutations.
Exclusion criteria	None stated
Number patients at baseline	n=24
Age at baseline	Not stated
Gender (n, % female) at baseline	Not stated
Tumour site at baseline	Retroperitoneal or abdominal
Disease status at baseline	Not stated
Tumour size at baseline	Not stated
Tumour grading at baseline	Not stated
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Fibrosarcoma n=5 (28%), Mixofibrosarcoma n=2 (11%), Synovial sarcoma n=3 (16,6%), Leiomyosarcoma n=3 (16,6%), Epithelioid Sarcoma n=2 (11%), Angiosarcoma n=3 (16,6%)
WHO performance status	Not stated
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	Chemotherapy + regional hyperthermia Note: Judged by the clinical experts as palliative care.

General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: EHY-2000 Target tumour temperature: 41,5-42°C Planned dosage: 60min Planned sessions: U Achieved tumour temperature: U Achieved dosage: U Achieved sessions: U
Detailed description of chemotherapy	Ifosfamide 3000mg/m^2 and Mesnum for uroprotection, day 1–3 and repeated at day 21
Detailed description of radiotherapy	Not stated
Detailed description of surgery	Not stated
Description of any other concomitant treatments	Ondansetron, dexamethasone, lorazepam, prochlorperazine were administered as premedication
Adverse events	CTC criteria Complications related to chemotherapy (expressed as % of patients with the complication, no absolute numbers given) anemia G3=10% neutropenia G3=40%, G4=20% thrombopenia G3=2% neurlogical toxicity 9% Hyperthermia related (expressed as number of patients with the complication) Bolus pressure G2=4 Pain related to position G2=3
Follow-up period	Not stated
Withdrawals (patients who withdrew from the study after enrollment with reason)	n=6 (four patients had their treatment stopped due to low performance status and two patients were not accounted for)
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: (Serious) inherent to design. 2.Bias in selection of participants into the study: (NI) No information is reported about selection of participants. 3.Bias in classification of interventions: (NI) Insufficient information is reported about this. 4.Bias due to deviations from intended intervention: (NI) No information is reported about this. 5.Bias due to missing data: (Serious) 24 patients enrolled and 18 patients reported on. 6.Bias in measurement of outcomes: (Moderate) Objective outcomes and use of an explicit grading system. 7.Bias in selection of the reported result: (NI) No protocol information available.

First author	**Wendtner**
Year of publication	2001
Clinical trial identification number	Not stated
Sponsorship source and role of funder	Supported by the Deutsche Krebshilfe and the European Society for Hyperthermic Oncology (ESHO).
City, Country of patient recruitment	Munich, Germany
Setting	Not stated
Article language	English
Declaration of interest	Not stated

Contact with authors	Contacted but without response
Study design	Prospective single arm trial
Choice of analysis set	Not stated
Inclusion criteria	Histologically-confirmed STS without manifestation of distant disease. only tumours with grade II or III histology, size 55cm, extracompartmental and deep extension Patients with primary STS, as well as with recurrent or inadequately-resected tumours, with or without attempts of radiotherapy
Exclusion criteria	Previous chemotherapy
Number patients at baseline	n=54
Age at baseline	Median 43y, range 18–75y
Gender (n, % female) at baseline	n=21, 39%
Tumour site at baseline	Trunk n=7 (13%), abdomen/pelvis n=28 (52%), extremity n=19 (35%)
Disease status at baseline	Surgery and/or radiation n=36 67%
Tumour size at baseline	Median ellipsoidal tumour volume=240cc
Tumour grading at baseline	G2=33, G3=21
Tumour depth at baseline	Not stated
Sarcoma histological subtype	Liposarcoma n=12 (22%), Leiomyosarcoma n=11 (20%), Malignant fibrous histiocytoma n=9 (17%), Malignant schwannoma n=5 (9%), Angiosarcoma n=3 (6%), Synovial sarcoma n=2 (4%), Rhabdomyosarcoma n=2 (4%), Extraskeletal Ewing's sarcoma n=2 (4%), Others n=8 (15%)
WHO performance status	median=1
TNM-stage	Not stated
AJCC prognostic stage group	Not stated
General description of intervention	>4 courses of neoadjuvant chemotherapy and regional hyperthermia, every 3 weeks >followed by surgery if possible >adjuvant treatment for patients without progressive disease after neoadjuvant treatment, including four adjuvant courses of chemotherapy without hyperthermia. Not pre-irradiated patients received radiotherapy
General description of comparator	Not applicable
Detailed description of hyperthermia	Hyperthermia Device: BSD-2000 Target tumour temperature: Tmax ≥42°C Planned dosage: 60 min Planned sessions: 8 Achieved tumour temperature: Tmax 42,2°C (mean) T90 39,3°C (median) Achieved dosage: U Achieved sessions: 8 (median), range 2-8
Detailed description of chemotherapy	doxorubicin 50 mg/m^2, etoposide 125mg/m^2, ifosfamide 1500 mg/m^2
Detailed description of radiotherapy	External beam radiotherapy using mega-voltage for patients who were not pre-irradiated, total dose in the range of 55–65 Gy in daily fractions (1.8–2.0 Gy) (not clear if radiotherapy was given (neo)adjuvantly.
Detailed description of surgery	A wide excision with preservation of function was primarily attempted during surgery.
Description of any other concomitant treatments	Not stated
Adverse events	CTC grade Maximal toxicity during neoadjuvant chemotherapy with regional hyperthermia (expressed as number of patients with AE) Leucopenia G0=– G1=– G2=6 G3=28 G4=20 Thrombocytopenia G0=16 G1=30 G2=5 G3=3 G4=– Nausea G0=8 G1=29 G2=15 G3=2 G4=– Vomiting G0=28 G1=15 G2=11 G3=– G4=–

	Alopecia G0=– G1=1 G2=53 G3=– G4=– Infection G0=46 G1=5 G2=2 G3=– G4=1 Renal toxicity G0=51 G1=3 G2=– G3=– G4=– Neurotoxicity G0=42 G1=8 G2=3 G3=– G4=1 Cardiac toxicity G0=45 G1=7 G2=2 G3=– G4=– Fever of unknown origin G0=43 G1=7 G2=4 G3=– G4=– Acute reactions related to hyperthermia Skin burn none=48 mild to moderate=6 severe=– Subcutaneous tissue necrosis none=51 mild to moderate=3 severe=– Muscle necrosis none=47 mild to moderate=6 severe=1 Pain within the applicator none=44 mild to moderate=9 severe=1 Bolus pressure none=40 mild to moderate=9 severe=5 Localized infection none=54 mild to moderate=– severe=– Toxicity adjuvant treatment (n=27) nausea (n=unclear), infection G3 n=1, neurotoxicity G4 n=1, leucopenia G3=18%, G4=73% , severe thrombocytopenia G4=9%
Follow up period	median of 57 months (95% CI: 50.2–58.8 months)
Withdrawals (patients who withdrew from the study after enrollment with reason)	Postoperative protocol treatment was not given to 27 patients due to disease progression or refusal of further therapy
Any data on patient satisfaction, shared decision making measures, procedural time or resource use	Not stated
Risk of bias parameters	1.Bias due to confounding: inherent to design 2.Bias in selection of participants into the study: No information is reported about selection of participants 3.Bias in classification of interventions: Intervention status is well defined 4.Bias due to deviations from intended intervention: There were deviations from the intended intervention, but these reflect usual practice 5.Bias due to missing data: adverse events are reported for all patients 6.Bias in measurement of outcomes: Objective outcomes and use of an explicit grading system 7.Bias in selection of the reported result: No protocol information available

Abbreviations: U=Unclear, AE=adverse events

Table A4: Characteristics of other relevant studies

List of ongoing and planned studies

Table A5: List of ongoing studies with devices for regional hyperthermia

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
HYPROSAR NCT01904565	Not clear	Single arm trial	26	Superficial or deep hyperthermia + proton beam radiation	None	Adults with soft tissue sarcoma	Acute and late adverse events, Local response, Local disease free survival
HyperTET NCT02359474	Not clear	RCT	120	Chemotherapy + regional hyperthermia	Chemotherapy only	Adults with high-risk soft tissue sarcoma	Progression-free Survival, Overall Survival
UMIN000013056	Completed recruitment and data collection but unpublished results	Single arm trial	40	Radiotherapy + Chemotherapy + Hyperthermia	None	Patients 15-70y with soft tissue sarcoma	Overall survival, Local response, adverse events

List of excluded studies

Table A6: List of excluded studies with reasons

Study Identifier	Reason for exclusion
Aiba 2018 [211]	Other study design
Aiba 2018 [212]	Other study design

Study Identifier	Reason for exclusion
Amichetti 1996 [213]	Other patient population
Angele 2014 [100]	Other study design
Anonymous 2007 [214]	Conference Abstract about EORTC trial
Anonymous 2018 [215]	Background article
Braun 2018 [216]	Conference Abstract from study by Eckert 2018 (excluded study)
Brizel 1996 [217]	Other outcomes
Buecklein 2012 [218]	Conference Abstract about subgroup analysis for single arm study by Nickenig 2009
Cattari 2017 [219]	Conference Abstract, no full text identified, authors contacted without response, single arm trial that includes a mixed patient population
Cattari 2018 [220]	Conference Abstract, no full text identified, authors contacted without response, same study as reported in Cattari 2017
Craciunescu 2009 [221]	Other outcomes
Datta 2013 [222]	Conference Abstract about HYPROSAR trial (ongoing study)
Datta 2016 [223]	Conference Abstract about HYPROSAR trial (ongoing study)
de Jong 2012 [224]	Conference Abstract about a retrospective case series
De Jong 2012 [225]	Conference Abstract, no full text identified, authors contacted without response, single arm trial
Del Priore 2015 [226]	Conference Abstract, no full text identified, authors contacted without response, single arm trial including mixed populations
Dewhirst 2005 [227]	Other outcome

Study Identifier	Reason for exclusion
Di Dia 2016 [228]	Conference Abstract, no full text identified, authors contacted without response, single arm trial including mixed population
Eckert 2018 [229]	Other intervention
Eckert 2018 [230]	Other study design
Emami 1991 [231]	Other outcomes
Engin 1993 [232]	Other outcomes
Engin 1994 [233]	Other study design
Feldmann 1993 [234]	Other patient population
Fendler 2015 [235]	Other study design
Fendler 2015 [236]	Other study design
Feyerabend 1996 [237]	Other patient population
Garibaldi 2016 [238]	Conference Abstract, no full text identified, authors contacted without response, single arm trial with mixed population
Gilden 1995 [239]	Other patient population
Goldobenko 1996 [240]	Other outcomes
Hiraoka 1994 [241]	Other patient population
Hiraoka 1995 [242]	Other patient population
Hohenberger 1999 [243]	Other study design

Study Identifier	Reason for exclusion
Issels 1990 [244]	Other patient population
Issels 1999 [245]	Background article
Issels 1995 [246]	Other study design
Issels 1999 [247]	Conference Abstract from study by Issels 2001 (included study)
Issels 1993 [248]	Other outcomes
Issels 1993 [249]	Other patient population
Issels 2012 [250]	Conference Abstract about subgroup analysis for EORTC trial (included study)
Issels 2010 [251]	Conference Abstract about subgroup analysis for EORTC trial (included study)
Issels 2010 [252]	Other comparator
Issels 2011 [253]	Conference Abstract about subgroup analysis for EORTC trial (included study)
Issels 2015 [254]	Conference Abstract about EORTC trial
Issels 1991 [255]	Other patient population
Issels 1990 [256]	Other patient population
Issels 2002 [257]	Background article
Issels 2009 [258]	Conference Abstract presenting data of the EORTC trial that is covered by EORTC 2010 (included study)
Ivanov 2005 [259]	Other patient population

Study Identifier	Reason for exclusion
Kang 2017 [260]	Other study design
Leopold 1992 [261]	Initial results for study that is covered by Prosnitz 1999 (included study)
Lindner 2004 [262]	Conference Abstract with initial results of the EORTC trial (included study)
Linthorst 2013 [263]	Other study design
Lopez-Pousa 2016 [264]	Other study design
Maar 2000 [265]	Other study design
Maluta 2018 [266]	Conference Abstract, author confirmed that no full text is available for this study, single arm trial with mixed population
Mitsumori 1996 [267]	Other outcomes
Myerson 1990 [268]	Other patient population
Myerson 1999 [269]	Other patient population
Nakano 1998 [270]	Other study design
Nickenig 2009 [271]	Conference Abstract, no full text identified, authors contacted without response, single arm trial
Otsuka 2001 [272]	Other study design
Park 2013 [273]	Background article
Roussakow 2017 [14]	Background article
Roussakow 2019 [274]	Background article

Study Identifier	Reason for exclusion
Sakurai 2001 [275]	Other outcomes
Schlemmer 2010 [201]	Other study design
Scully 1994 [276]	Initial results for study that is covered by Prosnitz 1999 (included study)
Shiga 1997 [277]	Other patient population
Siegmund-Schultze 2018 [278]	Conference Abstract providing data for EORTC trial that is covered by EORTC 2010/2018 (included study)
Stahl 1997 [279]	Other patient population
Stubbe 2016 [280]	Other study design
Sun 2019 [281]	Background article
Tejedor 2001 [282]	Other patient population
Tsukiyama 1990 [283]	Other patient population
Tsukiyama 1994 [284]	Other study design
Uno 1993 [285]	Initial results for study that is covered by Uno 1995 (included study)
Vidal-Jove 2016 [286]	Conference Abstract, no full text identified, authors contacted without response, single arm trial with mixed population
Vogl 1999 [287]	Other patient population
Wendtner 2002 [202]	Other study design
Wendtner 2000 [288]	Conference Abstract about study that is covered by Issels 2001(included study) and Wendtner 2001(included study)

Study Identifier	Reason for exclusion
Wessalowski 2003 [289]	Other outcomes
Xiao 2012 [290]	Conference Abstract, no full text identified, authors contacted without response, single arm trial

Risk of bias tables

Table A7: Risk of bias – study level (RCTs)

Trial	Random sequence generation	Allocation concealment	Blinding			Incomplete outcome data	Selective outcome reporting	Other Bias	Risk of bias – overall judgement
			Patient	Treating person	Outcome assessor				
EORTC trial	L	L	H [1]	H [1]	H [2]	L [3]	H [4]	L	H [5]

Footnotes:
1 Participants and personnel were not blinded for the allocated treatment. There is a difference in the number of patients that received post-induction chemotherapy. The authors state that this is driven by the effect of the induction therapy because progress or death during induction therapy implies no post-induction chemotherapy.
2 There was no blinding of the outcome assessors for the outcomes. For the Objective response rate outcome, an independent external review confirmed the judgements from the investigators but only for those classified as complete/partial response. There is a risk for misclassifications for patients that received the classifications “stable disease”, “progressive disease”, “could not be evaluated”.
3 Small amount of drop outs in both arms because of patients that withdrew consent. For the objective response rate, 97 out of 341 patients had the status “no measurable disease at randomisation” and these were not included in the analysis for this outcome.
4 While the trial protocols planned to evaluate overall survival, the 2018 paper reports only on disease-specific survival. The authors explain that "owing to the fact that our study comprises a 20-year data set that included an older age group between 41 to 70 years that represented more than 70% of the patients, there was an increasing risk of death from natural causes unrelated to sarcoma. Therefore, the survival benefit has been analyzed as death due to disease or its treatment so to be not confounded by the occurrence of disease-unrelated deaths." Relapse free survival was stated as a secondary outcome in the clinicaltrials.gov protocol, but not reported. We note that the 2015 Datecan guidelines for time-to-event end point definitions in sarcomas in Cancer trials considers relapse-free survival as an irrelevant/ambiguous end point. The full trial protocol also mentioned time to progression. The result of definitive surgery was not stated in the clinicaltrials.gov protocol, but this was mentioned in the full trial protocol.
5 High risk based on No judgements for blinding and Unclear judgements for selective outcome reporting and incomplete outcome data

Abbreviations: L= Low Risk, H= High Risk, U=Unclear

Table A8: Risk of bias – outcome level (RCTs)

Endpoint EORTC Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects increasing risk of bias	Risk of bias – outcome level
Overall survival	H	L[1]	L[4]	H[5]	L	H[6]
Disease specific survival	H	H[2]	L[4]	H[5]	L	H[6]
Progression-free survival	H	H[2]	L[4]	H[5]	L	H[6]
Amputation	H	L[1]	U[4]	L	L	H[6]
Severe to life-threatening AE	H	L[3]	H[4]	L	L	H[6]

Death from adverse events	H	L[1]	H[4]	L	L	H[6]

Footnotes:
1 Objective outcome for which no blinding of outcome assessors is required.
2 No blinding of outcome assessors for outcomes that require judgement.
3 Adverse events according to the CTCAE framework.
4 The authors stated that they used ITT for the effectiveness outcomes. An as-treated analysis was used for the safety outcomes. See also footnote 3 in Table A8.
5 While the trial protocols planned to evaluate overall survival, the 2018 paper reports only on disease-specific survival which was not planned in the initial protocol. See also footnote 4 in Table A8.
6 High risk of bias based on unclear judgements for all outcomes and no judgements for Disease-specific-survial and progression-free-survival.

Abbreviations: Y=Yes / N= No / U=Unclear, L= Low Risk / H= High Risk, AE= adverse events

Table A9: Risk of bias – outcome-level of single-arm trials about regional hyperthermia

Trial	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Adverse events								
Baur 2003	S[1]	NI	L	L	L	M[5]	NI[6]	S[8]
Fiegl 2004	S[1]	NI	L	L	L	M[5]	NI[6]	S[8]
Hayashi 2015	S[1]	NI	L	L	L	M[5]	M[7]	S[8]
Issels 2001	S[1]	NI	L	L	L	M[5]	NI[6]	S[8]
Maguire 2001	S[1]	NI	L	L	S[3]	L	NI[6]	S[8]
Makihata 1997	S[1]	NI	L	L	L	L	NI[6]	S[8]
Prosnitz 1999	S[1]	NI	L	M[2]	NI[4]	M[5]	NI[6]	S[8]
Uno 1995	S[1]	NI	L	L	L	M[5]	NI[6]	S[8]
Volovat 2014	S[1]	NI	NI	NI	S[9]	M[5]	NI[6]	S[8]
Wendtner 2001	S[1]	NI	L	L	L	M[5]	NI[6]	S[8]

Footnotes:

1 Risk of bias due to confounding is inherent to single arm design.
2 Changes to the hyperthermia protocol midway in the trial
3 Only patients with heatable tumours were evaluated for treatment-induced toxicity.
4 Not clear if there were missing data.
5 Grading of adverse events according to a grading system.
6 No study protocols available for verification.
7 Published protocol that states that adverse events would be recorded, but without further details about which adverse events.
8 Serious because of single arm design.
9 Serious because 24 patients enrolled and 18 patients reported on.

Abbreviations: L=Low / M=Moderate / S=Serious / C=Critical / NI=No information

Table A10: Summary of findings tables

Effectiveness

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
EORTC trial (median follow-up 3y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	169	172	HR 0.88 (0.64, 1.21) Survival 2y RR 1.08 (0.96, 1.22) Survival 4y RR 1.04 (0.87, 1.24)	Median survival I=6.6y (4.5, >10) vs C=6.1y (3.8, >10), AD 0.5y Survival 2y RD 6% (-3, 15) Survival 4y RD 2% (-8, 13)	Low	Critical
EORTC trial (median follow-up 11y)	Randomised trial	Serious[1]	-[2]	Not serious	Not serious	None	162	167	Deaths RR 0.89 (0.74, 1.07)	Deaths RD -7% (-17, 4)	Low	Critical
Disease specific survival												
EORTC trial	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	162	167	HR 0.73 (0.54, 0.98)		Low	Critical

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
(median follow-up 11y)									Survival 5y RR 1.22 (1.01, 1.48) Survival 10y RR 1.23 (0.98, 1.55)	Median survival I=15.4y (6.6, >17.0) vs C=6.2y (3.2, 10.3), AD 9.2y Survival 5y RD 11% (1, 22) Survival 10y RD 10% (-1, 21)		
Disease-free survival[4]												
EORTC trial (median follow-up 3y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	169	172	DFS 2y RR 1.31 (1.06, 1.62) DFS 4y RR 1.20 (0.92, 1.58)	DFS 2y RD 14% (3, 24) DFS 4y RD 7% (-3, 17)	Low	Critical
EORTC trial (median follow-up 11y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	162	167	HR 0.71 (95% CI 0.55, 0.93)	Median DFS I=2.8y (2.0, 4.9), C=1.5y (1.1, 2.1), AD 1.3y	Low	Critical
Progression-free survival[4]												
EORTC trial (median follow-up 3y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	169	172	PFS 2y RR 1.25 (1.08, 1.45) PFS 4y RR 1.20 (1.01, 1.43)	PFS 2y RD 15% (6, 25) PFS 4y RD 11% (1, 21)	Low	Critical

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
EORTC trial (median follow-up 11y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	162	167	HR 0.65 (0.49, 0.86)	Median PFS I=5.6y (2.9, 8.7) C=2.4y (1.7, 4.2), AD 3.2y	Low	Critical
Amputation												
EORTC 2010 (median follow-up 3y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	104[5]	102[5]	RR 0.76 (0.29, 1.95)	RD -2% (-10, 5)	Low	Critical
EORTC trial (median follow-up 11y)	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	80[5]	86[5]	RR 0.84 (0.33, 2.14)	RD -2% (-11, 7)	Low	Critical
Health-related quality of life												
Outcome not assessed												Critical
Pain												
Outcome not assessed												Critical
Objective response rate												
EORTC 2010 (median follow-up 3y)	Randomised trial	Serious[1]	-[2]	Not serious	Not serious	None	118[6]	126[6]	RR 2.27 (1.31, 3.89)	RD 16% (6, 26)	Low	Important
EORTC trial (median	Randomised trial	Serious[1]	-[2]	Not serious	Serious[3]	None	162	167	RR 2.31 (1.35, 3.95)	RD 17% (7, 27)	Low	Important

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
follow-up 11y)												
Fatigue												
Outcome not assessed												Important
Motor function												
Outcome not assessed												Important
Neurological function												
Outcome not assessed												Important
Psychological wellbeing of patients												
Outcome not assessed												Important
Rate of local tumour control												
Outcome not assessed												Important
Local tumour recurrence												
Outcome not assessed												Important
comments: 1 Downgraded because of limitations in study design. 2 Unable to evaluate because there is only one RCT. GRADE suggests especially careful scrutiny of all relevant issues when only a single RCT addresses a particular question.[32] 3 The 95% confidence interval presents a large imprecision. 4 The survival benefit has been analyzed as overall survival at the 3y follow up and as death due to disease or its treatment at the 11y follow-up. 5 Denominator is patients that received definitive surgical resection 6 Denominator is patients with measurable disease												

Abbreviations: CI Confidence Interval; I Intervention; C Comparator; DFS Disease-free survival; PFS Progression-free survival; HR Hazard ratio; RD Risk difference; AD Absolute difference

Safety

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Im-precision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Death related to adverse events												
EORTC trial median follow-up 11.3y	Randomised trial	Serious[1]	Not serious	Not serious	Serious [2]	None	162	169	RR 2.58 (0.51, 13.09)	RD 2% (-1, 5)	Low	Critical
2 studies Follow-up range 1-17.6y	Single arm trials	Serious[3]	Not serious	Not serious	Serious[4]	Serious[5]	103	none	-	I=0% (0, 46) I=3% (1, 9)	Very low	Critical
Severe to life-threatening AE (grade 3 to 4)												
EORTC trial (median follow-up 3y)	Randomised trial	Serious[1]	Not serious	Not serious	Serious[2]	Serious[7]	162	169	Severe to life-threatening AE in following categories: haematological toxicities, nephrotoxicities, cardiotoxicities, neurotoxicities, gastrointestinal toxicities, infections, musculoskeletal and connective tissue disorders, injuries and general disorders as described in Table 6-2		Very Low	Critical
10 studies	Single arm trials	Serious[3]	Serious[6]	Not serious	Serious[4]	Serious[5]	312	none		Severe to life-threatening AEs present in every study AE/patient 0.23-1.8 (2 studies) Range patients with AE 14-100% (2 studies)	Very low	Critical

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Im-precision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
										Amputation due to AE (2 studies) I= 4% (1, 10) I= 7% (0, 34)		

comments:

1 Downgraded because of limitations in study design described in the risk of bias table for RCTs.
2 The 95% confidence interval presents a large imprecision.
3 Downgraded because of limitations in study design described in the risk of bias table for non-randomised studies.
4 Downgraded because of wide confidence intervals for the reported adverse events.
5 Downgraded because of risk for publication bias (completed but not published study and 10 potentially relevant conference abstracts without full text) and downgraded because of partial reporting of adverse events which do not cover all the treatment components.
6 Downgraded because of heterogeneity in frequencies for the reported adverse events.
7 Downgraded because of partial reporting of adverse events which do not cover all the treatment components.

Abbreviations: CI Confidence Interval; I Intervention; C Comparator; AE Adverse event; RR Relative risk, RD Risk difference

Other outcomes

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Patient satisfaction												
Outcome not assessed												Important
Shared decision making measures												
Outcome not assessed												Important
Resource use												
Outcome not assessed												Important
comments: none												

Applicability tables

Table A11: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population for this assessment were adults (>18yrs) who have a high-risk STS. This was defined as a high-grade tumour, situated deep to the subcutaneous fascia and large (size > 5cm). We focused on both localized and metastatic sarcomas and we included patients undergoing curative treatment and patients undergoing palliative treatment. The characteristics of the patients enrolled in the included studies match well with the targeted population for curative hyperthermia treatment. Uno 1995 and Volovat 2014 were the only studies that focused on patients undergoing palliative treatment. The studies have patient groups with median and average ages in the 50s. Ages typically ranged from 18 years to 80 years, with 89 years at the upper end. The gender distribution in the studies is balanced (44% female). The studies included large tumours with diameters of over 5 cm for all or most of the patients.[29, 30, 57, 58, 60] Other studies reported mean tumour volumes of 251 cm^3 and 1668 cm^3 or median volumes of 240 cc and 300 cc.[55-57, 59] In three studies, tumour size was not reported.[31, 54, 61] Tumour grading at baseline was grade 2 for 46% (n=249) of the patient population, grade 3 for 53% (n=286) and an unspecified high grade for 1% (n=4). Three studies did not provide information on the tumour grading.[30, 59, 61] Depth of the tumour and TNM stage were poorly reported across the included studies. Overall, the studies included an equal number of tumours located in the extremities or non-extremities. Hayashi 2015 included extremity tumours only. Fiegl 2004 and Volovat 2014 included non-extremity tumours only. Liposarcoma (20%) and undifferentiated pleomorphic sarcoma (20%) were the most frequent histological sarcoma type, followed by leiomyosarcoma (14%) and synovial sarcoma (9%). A large group of sarcomas was not further specified (28%). A small number of tumours might not have been soft-tissue tumours (1%). Six studies included patients with non-metastatic disease.[29, 30, 55, 58-60] Three further studies stated that they excluded patients with distant metastatic disease.[30, 56, 57] One study included metastatic patients only.[61] One study included both metastatic and non-metastatic patients.[54]

Domain	Description of applicability of evidence
Intervention	The targeted intervention for this assessment was regional application of non-invasive external hyperthermia to a STS and administered in addition to chemo- and/or radiotherapy and treatment as usual. This assessment included the use of hyperthermia in both a neoadjuvant and adjuvant context and in situations in which hyperthermia is used without surgical resection. We accepted the treatment temperature to be in the range of 39 to 45°C in accordance with both ESHO and the Kadota Fund International Forum guidelines. Overall, the studies included in this assessment adequately reflect the targeted parameters. Five studies applied hyperthermia in combination with chemotherapy and radiotherapy,[29, 31, 57, 59, 60] four studies applied hyperthermia combined with chemotherapy [54-56, 61] and two studies applied hyperthermia together with radiotherapy.[30, 58] Five studies used hyperthermia as a neoadjuvant treatment,[30, 54, 55, 58, 59] in one study hyperthermia was used adjuvantly [31] and three studies used hyperthermia both neoadjuvantly and adjuvantly.[29, 56, 57] Six studies used the BSD-2000 device,[29, 30, 54-57] two studies used Thermotron RF-8,[31, 60] one study used both the BSD-1000 and the HEH-500C devices[59] and one study used the EHY-2000 device. The BSD devices and the EHY-2000 device have CE approval but not the Thermotron RF-8 and HEH-500C devices. No eligible studies were identified for the other CE-approved devices. All the studies targeted tumour temperatures within the predefined range, although two studies reported maximum temperatures above 50°C.[58, 59]
Comparators	The EORTC RCT used neoadjuvant chemotherapy and adjuvant radiotherapy as the comparator treatment. This reflects the prevailing usual care within the period of the trial.
Outcomes	The RCT reported on the following effectiveness outcomes: overall survival, disease-specific survival, disease-free survival, progression-free survival, amputation and objective response rate. The median follow up time was 11.3 years, range 9.2–14.7 years. This includes most of the outcomes that the assessment team considered critical to decision-making. The assessment team also rated the following outcomes as critical: Health-related quality of life, Pain – although these were not evaluated in the RCT. Prosnitz 1999, Uno 1995, Maguire 2001 and Volovat 2014 reported on adverse events for each treatment component. The other studies reported on hyperthermia-related adverse events and some of the other treatment components. Surgery-related adverse events were least reported. Some studies reported on acute toxicities only. Reporting on acute or late toxicity was generally poor. Seven studies used the CTCAE grading system, Maguire 2001 graded the adverse events according to RTOG guidelines, Baur 2003 applied a non-defined grading system and Prosnitz 1999 and Makihata 1997 did not grade the adverse events. Follow-up times ranged from eight months to 17.6 years. For Maguire 2001 and Volovat 2014, the follow-up duration was not clear. Other predefined outcomes that the assessment team rated as important to decision-making, i.e. fatigue, motor function, neurological function, psychological well-being, patient satisfaction, measures for shared decision making and resource use were not measured in the included studies.
Setting	The RCT took place in nine centres in four countries (six centres in Germany, one in Norway, one in Austria, one in the USA). Four single-arm trials were conducted at one centre in Germany,[29, 54-57] three studies took place in three different centres in Japan,[31, 59, 60] two studies were conducted in one centre in the United States[30, 58] and one study was conducted in Romania.[61] Two studies reported that patients were hospitalized for 6–8 days during each cycle of chemotherapy and hyperthermia.[29, 55] Two studies reported that they included inpatients.[29, 31] The other studies made no reference to the hospitalization status of patients during treatment.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A12: Regulatory status

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
EHY3010ML	EU US	CEE FDA	YES NO	Deep-seated primary tumours and metastasizes in organs (incl. liver, pancreas, kidney, lung, brain, etc.); gastroenterological tumours, including small and large intestine, stomach, esophagus, etc.; deep-seated gynaecological cases; sexual organs	Patient under deep-sedation or anaesthesia (missing thermal sensitivity). Application of analgesics in the treated area is prohibited; cannot be used when the patient is unconscious, not able to communicate with the Physician and operator; do not use the electrodes in the vicinity of the patient's metallic/prosthesis (bone-replacement, joint support, etc.) or patient's silicone prosthesis (breast implant.). The distance between the implanted metal and the circumflex of the upper electrode shall be more than the radius of the electrode; Before the treatment all metallic pieces (necklaces, rings, jewels, watches, pipes, coins, phones, hairpins, pens, etc.) have to be left far away from the treatment bed. Do not treat patients who have earphones, hearing-aid, music devices (Walkman, walk-watch, etc.) and or/any wire-connected instruments. Must have extra attention and care in addition emergency preparations for treating patients who have pacemaker or any other type of electrical implants (e.g. implanted. deep brain stimulator (DBS), implanted hearing-aids, im-	NF	Yes	NF
EHY 2000 Plus	EU US	CEE FDA	YES NO	Glioblastoma; oesophageal cancer; gastric cancer; liver cancer; cancer of kidney and renal pelvis; cervical cancer; pancreatic cancer; breast cancer; lung cancer. Their performances are also supported with clinical experience in the following indications: bladder cancer; prostate cancer; colorectal cancer		NF	Yes	NF
EHY 2030	EU US	CEE FDA	YES NO			NF	Yes	NF

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
					planted erectile function stimulator, etc.). Treating patients with pacemakers out of standards (not with 13.56MHz frequency) is not recommended and could be dangerous. Must not be used in case of tendency to haemorrhage, including menstruation or open wound (e.g. newly operated patients). Do not apply for person with organ-transplants or for patients who is suffering of consequences of organ-transplant. Cannot be used for patients who are not able to operate the emergency button.			
Celsius TCS	EU US	CEE FDA	YES NO	Gynaecological malignancies (e.g. breast, ovary, cervix etc.); malignant tumours in organs; deep seated cancer lesions (e.g. brain, liver, lung, kidney, pancreas, etc.); lymph node metastases; gastrointestinal tumours (oesophagus, colon, etc.); sarcomas, melanomas, basaliomas, etc. For the following tumours have been identities in the literature sufficient scientific evidence for: sarcoma; breast tumour; cervical tumour; extracranial germ cell tumour; rectal tumour. The following tumour types were already treated with the Celsius TCS system without	Pregnancy; metal implants or components; electrical components in the RF field; active implants; disturbed perception of temperature; unstable cardiovascular system; patients with a bone marrow or stem cell transplant; open wounds; scar tissue, damaged skin; tattoos with metallic pigments; epilepsy; patient under anaesthesia.	NF	Yes	NF

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
				having still knowledge of sufficient scientific publications: pancreas tumour; nasopharyngeal tumour.				
RF 1200 S	EU US	CEE FDA	YES NO	Limbs, Head & Neck, Colon, Liver, ,Sexual organs, Pancreas, Pelvis, Pleura, Lung, Kidney, Stomach, Bones		NF	Yes	NF
ALBA ON 4000	EU US	CEE FDA	YES NO	Melanoma, Breast tumours, Head & neck tumours, Sarcoma, Recurrent tumours, Lymphoma, Skin metastasis	Patients with: prosthesis and/or metallic implants near the part to be treated; implanted electrodes; pacemakers; haemorrhagic or thrombosis diseases; serious cardiac failure (i.e.: angina pectoris); pregnant women; children (growth cartilages). In the following cases, but under the regular supervision and responsibility of specialized medical personnel, carrying out a microwave hyperthermia treatment is possible paying special attention to any side effect and stopping the treatment if something occurs: patients with reduced thermal sensitivity; patients with severe dermatological diseases near the area to be treated; patient with ischemic tissues; obese patients.	NF	Yes	NF
ALBA 4D	EU US	CEE FDA	YES NO	Cervical cancer, Vaginal cancer, Vulva cancer, Ovarian cancer, Rectal cancer, Bladder cancer NMI, Bladder cancer MI, Soft tissue sarcoma, Prostate cancer, Oesophageal cancer, Pancreatic cancer,	Patients with: pacemakers; implantable cardiac defibrillators (ICD); unstable angina pectoris (under treatment) with threats of impending heart attack; hip replacement; reduced thermal sensitivity; pregnant women; patients in	NF	Yes	NF

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
				Paediatric tumours, Peritoneal Carcinoma-tosis	which intratumoral or intralu-minal temperature sensors cannot be placed. Relative contraindications to the use of hyperthermia are: hypertensive patients (dias-tolic blood pressure> 100mmHg and / or systolic blood pressure> 180 mmHg in treated patients); patients with arrhythmia who need therapy; patients with hypotension (di-astolic blood pressure <50mmHg and / or systolic blood pressure <90mmHg in patients undergoing treat-ment); patients with severe pulmonary disorders with a forced expiratory volume (FEV) <50%; patients with se-vere cerebrovascular diseases (multiple cerebrovascular acci-dents (CVA) or CVA in the 6 months prior to the start of treatment); cardiac frequency> 90 bpm; myocardial infarction within 6 months prior to initia-tion of treatment; known de-crease of circulation in the heated area (vasoconstrictive drugs, ischemia, disseminated intravascular coagulation or other causes); patients with any of the following in corre-spondence with the area to be treated, should be evaluated on a case-by-case basis: • Silicone implants. • Saline solution implants. • Stents. • Patients with foreign objects implanted or attached to the body.			

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
BSD 500	EU US	CEE FDA	YES YES	Recurrent or progressive cancerous tumours located within a few centimetres of the surface of the body. Interstitial hyperthermia is used to treat recurrent or progressive cancerous tumours located below the skins surface.	Because the patient's ability to detect pain is an essential safety mechanism, hyperthermia is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, regional or general anaesthetic, or other condition). Since excessive heating of normal tissue is prevented by normal blood perfusion, it is imperative that adequate circulation be present and maintained in all tissues within the heating field. Treatment is contraindicated in patients having known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause). Because electromagnetic radiation from the applicators of the device may interfere with the operation of an electronic device, hyperthermia treatments are contraindicated in patients with cardiac pacemakers.	NF	Yes	NF
BSD2000 3D/MR	EU US	CEE FDA	YES YES†	Locally advanced tumours of the cervix, bladder, and rectum	Patients who have implanted, worn or carried medical devices, including cardiac pacemakers, implanted defibrillators, infusion pumps, insulin pumps, cardiac monitoring electrodes and devices, deep brain stimulators, cochlear implants, radiofrequency identification devices attached to devices, or any other implanted active electronic device or	NF	Yes	NF

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
					monitoring system; patients with a body diameter > 49 cm from left to right; patients with severe dysfunction of the heart or lungs; patients with severe pulmonary disease with a forced expiratory volume (FEV) <50%; patients who cannot adequately respond to pain (those with significant neuropathies). patients who have had prior irradiation to the treatment site; patients who are less than 21 years of age; patients who have known decrease in circulation in the heated area produced by any means (i.e., vasoconstrictive drugs, DIC, ischemia or other cause); patients who have electrically conductive, metal, or foreign objects in or on or attached to their body; patients with unstable angina pectoris (under medication) with imminent threat of an infarction; patients with myocardial infarction < 6 months ago from treatment; patients with cardiac decompensation necessitating medication; patients with arrhythmia necessitating medication or an heart rate > 90 bpm; patients with hypertension: diastolic >100 mmHg and/or systolic >180 mmHg, while using medication; patients with hypotension: diastolic <50 mmHg and/or systolic <90 mmHg; patients with severe cerebrovascular disease: mul-			

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval	Launched yes/no	Approval number
					tiple cerebrovascular accidents (CVA) or a CVA < 6 months before treatment; patients with inability to place either an intratumoral or an intraluminal temperature sensor for monitoring of tumour indicative temperatures.			

† approved under HDE exemption for the treatment of cervical cancer

Abbreviations: NF = not found

Sources: user manuals/technical documents

Table A13: Summary of (reimbursement) recommendations in European countries for the technology

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Italy	Reimbursement provided for deep cancer hyperthermia for tumour treatment (induced by microwave ultrasound, low energy radiofrequency, interstitial probes or other means)	Not available
IQWiG - Germany	The method can be applied in the inpatient setting within the DRG flat rate but is not reimbursed in the outpatient setting (since 2005, the methods is included in the list of “overruled examinations or treatment methods”).	"Decision to include method in the list of “overruled examinations or treatment methods” (in German): https://www.g-ba.de/beschluesse/199/ German oncologists have coordinated the EORTC 62961-ESHO 95 Randomized Clinical Trial https://www.ncbi.nlm.nih.gov/pubmed/29450452, but these results have obviously not yet been incorporated in the national guidelines."
SNHTA - Switzerland	Use of hyperthermia is covered in cases with contraindication for chemotherapy. coverage is temporary and will be re-evaluated in 2020.	in German, French and Italian: https://www.admin.ch/opc/de/classified-compilation/19950275/201904010000/832.112.31.pdf
Netherlands	Reimbursement is provided for superficial hyperthermia in combination with radiotherapy regardless of the indication, and for deep hyperthermia in combination with radiotherapy for recurrent rectal carcinoma and advanced stage of cervical carcinoma.	Not available.

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
SHTG - Scotland	Procedure is not currently undertaken in Scotland and there are no plans for this to be introduced.	None.
VASPVT - Lituania	The treatment is not offered/reimbursed.	Not applicable.
Norway	Currently there is no reimbursement code available for the hyperthermia treatment.	Indicated for high-risk soft tissue sarcoma of extremities and trunk in adults, in particular cases of locally advanced, poorly resectable tumours. Feasibility of regional hyperthermia depends on individual technical applicability and patient factors.
Canary Islands - Spain	Not reimbursed.	Not applicable.
Austria	Hyperthermia is only offered in private settings.	Whether to introduce reimbursement for these treatments in public hospitals is currently debated.
England	Not covered by national guidance and therefore possible decision making would be local.	Not available.

Source: EUnetHTA survey

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
	There is evidence that socioeconomic characteristics of patients with soft tissue sarcoma have an impact on quality of healthcare and prognosis of the disease. Patients living in rural areas are at risk of having a reduced access to healthcare including regional hyperthermia.	
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	The use of devices for regional hyperthermia requires the establishment of specialised centres for administration.	
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes
	There is evidence of important financial and social impact for patients with a soft tissue sarcoma diagnosis. As a rare disease, this financial impact is much higher for the individual patient than for society. Intruduction of the new technology could increase these impacts.	
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
	The application of regional hyperthermia could require the use of a documented procedure-specific informed consent process, but this can vary across jurisdictions.	
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

Appendix 4: MISCELLANEOUS

Table A14: Overview of individual ratings for the importance of the outcomes for decision making

Outcome	Assessment team					Clinical experts		
EFFECTIVENESS	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**
Survival	9	9	9	9	9	9	9	9
Disease-free survival	8	9	6	4	8	7	9	9
Progression-free survival	8	8	8	4	7	5	9	9
Objective response rate	4	8	-	3	6	3	6	9
Health-related quality of life	7	8	7	8	7	5	6	6
Rate of local tumour control	6	7	-	3	6	5	6	8
Local tumour recurrence	6	7	8	3	6	5	6	9
Pain	7	7	5	7	7	5	5	8
Fatigue	6	6	2	6	6	3	4	5
Amputation	8	8	-	9	7	4	6	9
Motor function	7	6	5	8	6	4	6	8
Neurological function	7	5	6	8	6	4	5	8
Psychological wellbeing of patients	4	5	5	4	6	4	4	5
Psychological wellbeing of family and carers	3	5	3	1	3	3	3	1
Outcome **SAFETY**								
Mild to moderate AE (grade 1 to 2)	4	7	2	2	3	3	1	2
Severe to life-threatening AE (grade 3 to 4)	9	8	7	8	8	6	8	8
Death related to AE (grade 5)	9	9	9	9	9	9	9	9
Outcome **OTHER**								
Patient satisfaction	6	6	6	3	6	7	4	6
Shared decision making measures	3	4	-	-	5	7	2	5
Resource use	3	4	7	5	4	4	3	5
Procedural time	3	3	5	2	3	4	3	6

Table A15 Documentation of queries to study authors in the assessment report

Study	Content of query	Reply received yes / no	Content of reply
Cattari 2017	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Cattari 2018	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
De Jong 2012	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
De Priore 2015	▪ Inquiry about availability of full text for conference abstract	Yes	▪ No published manuscript available

Di Dia 2016	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Garibaldi 2016	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Maluta 2018	▪ Inquiry about availability of full text for conference abstract	Yes	▪ No full text available
Nickenig 2009	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Vidal-Jove 2016	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Xiao 2012	▪ Inquiry about availability of full text for conference abstract	No	▪ No reply
Maguire 2001	▪ Inquiry about various study characteristics	No	▪ No reply
Makihata 1997	▪ Inquiry about various study characteristics	No	▪ No reply
Hayashi 2015	▪ Inquiry about various study characteristics	No	▪ No reply
Baur 2003	▪ Inquiry about various study characteristics	No	▪ No reply
Uno 1995	▪ Inquiry about various study characteristics	No	▪ No reply
Issels 2001	▪ Inquiry about various study characteristics	No	▪ No reply
Wendtner 2001	▪ Inquiry about various study characteristics	No	▪ No reply
Fiegl 2004	▪ Inquiry about various study characteristics	No	▪ No reply
Prosnitz 1999	▪ Inquiry about various study characteristics	No	▪ No reply
Volovat 2014	▪ Inquiry about various study characteristics	No	▪ No reply
EORTC trial	▪ Inquiry about various study characteristics, about overall survival data at long term, and about hypothesis for higher number of deaths from treat-ment at long term.	Yes	▪ Reply with input for study characteristics, feedback that no analysis of overall survival is published.

Table A16 Overview of hyperthermia treatment related parameters of the included studies

Study	Hyperthermia Device	Target tumour temperature	Planned dosage	Planned sessions	Achieved tumour temperature	Achieved dosage	Achieved sessions
EORTC	BSD-2000	42°C	60 min	16	Tmax=41.8°C (median) T90=39.2°C (median)	60min at 40-42.5°C (author input)	Range 0-16
Invasive thermometry with catheter probes in different parts of the tumour Statement about adherence to 1998 ESHO guidelines							
Issels 2001	BSD-2000	Tmax ≥42°C	60 min	16	Tmax=42,5°C (mean) T90=39,8°C (mean)	U	preoperatively 8 (median), range 4–10 postoperatively 5 (median), range 2-8
Invasive thermometry with catheter probes in different parts of the tumour							
Wendtner 2001	BSD-2000	Tmax ≥42°C	60 min	8	Tmax 42,2°C (mean) T90 39,3°C (median)	U	8 (median), range 2-8
Interstitial thermometry							
Baur 2003	BSD-2000	Tmax ≥42°C	60 min (30 min preheating)	8	Tmax=42.5°C (mean) T90=38.9°C (mean)	U	U
Invasive thermometry with catheter probes in different part of the tumour							
Fiegl 2004	BSD-2000	Tmax = 42°C	60 min	U	Tmax=41°C (mean)	U	U
Invasive thermometry in the tumour region or superficial thermometry if intratumoural measurement was not possible							

Prosnitz 1999	BSD-2000	42,5°C	60min after reaching 42.5°C CEM 43°C T90 of 10-100	U	U	CEM 43° T90=32 min (extremities), 9min (non-extremities), 43min (2 sessions/week) protocol), 14 min (1 session/week) (medians)	U
Invasive thermometry with catheter probes in different parts of the tumour							
Maguire 2001	BSD-2000	Tmax=55°C	60-120min CEM 43°C T90 of 10-100	Max 10	U	CEM 43°C T90=90 min (mean) 38 min (median), range 0.1-601 min At thermal goal of CEM 43°C T90 ≥ 10 n=25	U
Interstitial thermometry Reference to US 1989 quality assurance guidelines from the Hyperthermia Committee of the American College of Radiology and the Hyperthermia Physics Center							
Uno 1995	Thermotron RF-8	U	45-60min	3-6	Tmax=range 41,1-43,0°C Taverage=range 40,0-42,4°C	U	3-6
Invasive thermometry with catheter probes in different parts of the tumour							
Makihata 1997	BSD-1000/ HEH-500C	>42°C	60 min	U	Tmax=43,4°C (mean),range 39.2-50.2°C Taverage=42,2°C (mean), range 38,9-47,8°C	Time ≥ 42°C= 280,6min, range 0-471min	8 (mean), range 4-14
Invasive thermometry with catheter probes in different parts of the tumour							

Volovat 2014	EHY-2000	41,5-42°C	60 min	U	U	U	U
No information available about thermometry							
Hayashi 2015	Ther-mo-tron RF-8	>42,5°C	60 min	5	U	U	4-5
Invasive thermometry with a thermocouple thermometer into scar tissue							

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the manufacturer(s) (fact check), as well as responses from the author, is available on the EUnetHTA website.