Author/s:
Ramamurthy, A;Connolly, EA;Mar, J;Lewin, J;Bhadri, VA;Phillips, MB;Winstanley, M;Orme, LM;Grimison, P;Connor, J;Lazarakis, S;Hong, AM;Omer, N;Cayrol, J

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High-dose chemotherapy for Ewing sarcoma and Rhabdomyosarcoma: A systematic review by the Australia and New Zealand sarcoma association clinical practice guidelines working party

Ashika Ramamurthy [a], Elizabeth A Connolly [b,c], Jasmine Mar [d], Jeremy Lewin [e,f], Vivek A Bhadri [b,c], Marianne B Phillips [g,h], Mark Winstanley [i], Lisa M Orme [f,j,k], Peter Grimison [b,c], Joanna Connor [l], Smaro Lazarakis [m], Angela M Hong [b,n,*], Natacha Omer [o,p,1], Julie Cayrol [j,k,q,1]

[a] Concord Repatriation General Hospital, Sydney Local Health District, Concord, NSW 2139, Australia
[b] Central Clinical School, Faculty of Medicine and Health, The University of Sydney, NSW 2006 Australia
[c] Department of Medical Oncology, Chris O'Brien Lifehouse, Camperdown, NSW 2050, Australia
[d] Australia and New Zealand Sarcoma Association, Parkville, Victoria 3010, Australia
[e] Department of Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia
[f] Victorian Adolescent & Young Adult Cancer Service, Melbourne, VIC 3000, Australia
[g] Department Oncology, Haematology and Tissue & Cellular Therapies, Perth Children's Hospital, WA 6009, Australia
[h] Telethon Kids Institute, Perth, WA 6009, Australia
[i] Starship Paediatric Blood and Cancer Centre, Central Auckland 1142, New Zealand
[j] Children's Cancer Centre, The Royal Children's Hospital Melbourne, VIC 3000, Australia
[k] Department of Paediatrics, The University of Melbourne, Parkville VIC 3052 Australia
[l] Te Pūriri o Te Ora, Auckland Regional Cancer and Blood Service, Auckland Hospital, Grafton, 1050, New Zealand
[m] Health Sciences Library, Royal Melbourne Hospital, Parkville, Victoria 3010, Australia
[n] Department of Radiation Oncology, Chris O'Brien Lifehouse, Camperdown, NSW 2050, Australia
[o] Oncology Services Group, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD 4101, Australia
[p] Frazer Institute, Faculty of Medicine, The University of Queensland, Woolloongabba, QLD, Australia
[q] Murdoch Children's Research Institute, Melbourne, Australia

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ABSTRACT

Introduction: Patients with high-risk or metastatic Ewing sarcoma (ES) and rhabdomyosarcoma (RMS) have a guarded prognosis. High-dose chemotherapy (HDT) with autologous stem cell transplant (ASCT) has been evaluated as a treatment option to improve outcomes. However, survival benefits remain unclear, and treatment is associated with severe toxicities.

Methods: A systematic review was conducted, using the population, intervention, comparison outcome (PICO) model, to evaluate whether utilization of HDT/ASCT impacts the outcome of patients with ES and RMS compared to standard chemotherapy alone, as part of first line treatment or in the relapse setting. Medline, Embase and Cochrane Central were queried for publications from 1990 to October 2022 that evaluated event-free survival (EFS), overall survival (OS), and toxicities. Each study was screened by two independent reviewers for suitability. A qualitative synthesis of the results was performed.

Results: Of 1,172 unique studies screened, 41 studies were eligible for inclusion with 29 studies considering ES, 10 studies considering RMS and 2 studies considering both. In ES patients with high-risk localised disease who received HDT/ASCT after VIDE chemotherapy, consolidation with melphalan-based HDT/ASCT as first line therapy conveyed an EFS and OS benefit over standard chemotherapy consolidation. Efficacy of HDT/ASCT using a VDC/IE backbone, which is now standard care, has not been established. Survival benefits are not confirmed for ES patients with metastatic disease at initial diagnosis. For relapsed/refractory ES, four retrospective studies report improvement in outcomes with HDT/ASCT with the greatest evidence in patients who demonstrate a

* Corresponding author.
E-mail address: angela.hong@sydney.edu.au (A.M. Hong).
[1] Senior co-authors.

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treatment response before HDT, and in patients under the age of 14. In RMS, there is no proven survival benefit of HDT/ASCT in primary localised, metastatic or relapsed disease.
Conclusion: Prospective randomised trials are required to determine the utility of HDT/ASCT in ES and RMS. Selected patients with relapsed ES could be considered for HDT/ASCT.

Introduction

Ewing sarcoma (ES) and rhabdomyosarcoma (RMS) are small round blue cell tumours that occur in children, adolescents and young adults (AYA) [1–3]. In ES, the EWSR1-FLI1 fusion is identified in 85 % of cases [1,4]. Small round cell sarcomas of bone and soft tissue where EWSR1-FLI1 fusion is not identified were previously collated with ES and termed the Ewing sarcoma family of tumours (ESFT) [1]. Molecular profiling has revealed fusions including EWSR1–non-ETS fusions, CIC-rearrangements, and BCOR alterations by which these tumours are now classified and understood to confer different natural histories and treatment sensitivities [5,6]. RMS is classified into a number of subtypes. The embryonal RMS (ERMS) and alveolar RMS (ARMS) subtypes typically occur in children and young adults while the pleomorphic subtype typically occurs in older adults [5,7]. The FOXO1-PAX3/7 gene fusion confers a poorer prognosis, is frequently found in ARMS (80–90 %) and distinguishes ARMS from ERMS [7].

Survival rates in localised ES and RMS have improved significantly in the last decades due to cooperative trial groups identifying effective multiagent systemic therapy and adequate local control, with contemporary trials reporting > 80 % survival in those with localized disease [8,9]. However, some patients have worse prognosis. As per the current body of evidence, adverse prognostic factors for localised ES (or 'high-risk' ES) include poor histological or radiological response to induction chemotherapy, and large tumour volume at diagnosis [10]. Adverse prognostic factors for RMS (or 'high-risk' RMS) include incompletely resected embryonal RMS occurring at unfavourable sites, age 10 years or older, tumour size larger than 5 cm, embryonal RMS with nodal involvement and alveolar RMS with or without nodal involvement [11,12]. Outcomes in primary disseminated multifocal ES, metastatic RMS and relapsed ES/RMS are poor with 5-year OS below 30 % [8,9,13].

For patients with metastatic or high-risk ES and RMS, high dose chemotherapy with autologous stem cell transplant (HDT/ASCT) has been postulated as an alternative to conventional chemotherapy, or to consolidate initial therapy. The rationale for HDT is to exploit the dose–response relationship with alkylating agents, where relatively small changes in dose may impact tumour cell kill in these highly chemosensitive tumours [10,14]. The relative benefit of HDT/ASCT, however, remains uncertain and must be balanced against the potential severe haematological and non-haematological toxicities and treatment-related mortality (TRM) associated with HDT.

In this systematic review, we aim to address the impact of HDT/ASCT in patients with ES and RMS on survival outcomes and treatment-related toxicities. This was conducted to inform the development of national clinical practice guidelines.

Methods

The Australia and New Zealand Sarcoma Association (ANZSA, www.sarcoma.org.au) guidelines working party utilised the following PICO (population, intervention, comparison, and outcome) model to evaluate the following question: *Does utilisation of HDT/ASCT have an impact on outcomes of patients with ES and RMS compared to standard chemotherapy alone a) as part of first line treatment? and b) in the relapse setting?*

1. **P**opulation: Patients of all ages with Ewing sarcoma (ES) and rhabdomyosarcoma (RMS)
2. **I**ntervention: High dose/myeloablative chemotherapy (HDT) with autologous stem cell transplant (ASCT)
3. **C**omparison: Standard chemotherapy (or no comparison group)
4. **O**utcomes: Overall survival (OS), event-free survival (EFS), treatment-related mortality (TRM) and toxicity

The ANZSA guidelines working group elected to evaluate ES and RMS, as these are the two main sarcoma subtypes in which HDT has been studied. Results are organised by sarcoma subtype but are reported together in order to highlight common themes and outcomes and with consideration that the treating physicians to whom this may be of interest, will frequently manage both subtypes. For outcome measures, 'EFS' was evaluated in screening as any event-related endpoint including, but not limited to, progression-free survival (PFS), disease-free survival (DFS) and failure-free survival (FFS) depending on which endpoint had been reported. The event-related endpoints varied between papers and have been reported in Table 1-5.

A literature search was performed in November 2021, and updated in October 2022, across multiple databases (Ovid Medline, Ovid Embase, and Cochrane Central (Wiley)) with inclusion and exclusion criteria constrained by the PICO framework and English language only (Supplementary Table 1). Due to a paucity of prospective, randomised, or large volume data, studies without a comparison group of standard chemotherapy were also included. The search strategy was developed with the help of a medical librarian (Supplementary Fig. 1). Key articles on the topic, MeSH terms and keywords were identified to refine the search strategy, which was then pilot tested and adapted to the different databases. Publications prior to 1990, case reports, conference abstracts, reviews and editorials were excluded, as well as studies pooling RMS/ES outcomes with other types of sarcomas. The abstract, full-text screening and data extraction were conducted in the Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at https://www.covidence.org). Studies were screened by title and abstract as per the PICO model, and against the inclusion and exclusion criteria by two independent reviewers. Selected full texts were then similarly screened to confirm inclusion. Conflicts were resolved through discussion with a third reviewer. The different screening phases and exclusion criteria are shown in the PRISMA flow chart (Fig. 1). Data was extracted in a Covidence custom-built data extraction template and verified by a second reviewer. The quality of each study was assessed by two independent reviewers using the NHMRC Evidence Hierarchy and Newcastle-Ottawa Quality Assessment Form for Cohort Studies or Cochrane Assessment Tool for Randomised Trials where appropriate (Supplementary Table 2) [15–17]. Conflicts were resolved through discussion with a third reviewer.

Results

After removal of duplicates, a total of 1,172 studies were identified from the search strategy for title and abstract screening. The inter-rater reliability for title and abstract screening was 90.6 % and 77.5 % for full text review. The selection process yielded a final number of 41 studies that addressed the impact of HDT/ASCT in ES and RMS. These included 29 ES studies, 10 RMS studies, and two studies including both ES and RMS. On quality assessment, four studies were randomised controlled trials [10,18,19] or pseudo-randomised [20] and were largely assessed as being of low risk of bias as per the Cochrane Collaboration's risk-of-bias tool for randomised trials (Supplementary Table 2) [21]. Of the

Table 1
Studies including primary Ewing sarcoma.

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Madero 1998	Retrospective case series	Multicenter	Spain	At least one of the following (1) metastatic disease at the time of diagnosis; (2) pelvic primary tumour; or (3) tumour volume > 100 mL in first CR	BuMel (n = 12); others	26.5 months	10.8yo (2–18)	20	DFS at time of study: 62.7 % (SD 11 %)	Basic
Paulussen 1998	Retrospective cohort study	Multicenter	Germany	Primary stage IV disease	Melphalan + etoposide +/- TBI +/- carboplatin; others	19 months	15yo (0.3–44)	171 (36 HDT)	4-year EFS: 0.23 % vs. 0.28 %, p = 0.982	Minimal
Marcus 2002	Retrospective cohort study	Monocentric	USA	Risk group according to size of primary tumour – high-risk (HR) > 8 cm or metastatic	Varied	Not stated	3-46yo	68 (HDT protocols HR2-HR5)/ 76 (HR1, SR1, SR2, various)	5-year OS: 63 % (HR3, HR4 – n = 32) vs. 53 % (SR1, SR2 – n = 26) in patients without detectable metastases at diagnosis	Minimal, TRM only
Drabko 2005	Retrospective case series	Two centers	Poland	Metastatic, poor local control in first CR (no surgery or poor histological response)	BuMel (n = 12); others (n = 9)	24 months (HDT in CR)	12yo (4.5–20)	21	2-year DFS: 0.68 if CR; <0.1 if not2-year OS: 0.63 if CR; 0.0 if not	Basic
Laurence 2005	Retrospective case series	Monocentric	France	High-risk localised disease (bulky tumour > 8 cm, inoperable tumour, or poor histological response), metastatic disease with PR or CR and no persistent bone marrow involvement	Mel + other agents; various	7.1 years	21yo (15–46)	46	5-year PFS: 47 % (SD 7.6 %) 5-year OS: 63 % (SD 7.1 %) 10-year OS: 60 % (SD 8 %)	Basic
Oberlin 2006	Single arm trial	Multicenter	France	Untreated metastatic bone disease	BuMel	8.2 years	12.3yo (2mo to 25y)	97 (75 HDT)	1-year EFS: 47 % (SD 11 %, HDT) vs. 37 % (SD 10 %, all patients) 10-year EFS: 43 % (SD 12 %, HDT)1-year OS: 38 % (SD 10 %, all patients)	Basic
Yamada 2007	Single arm trial	Single center	Japan	Primary high-risk ESFT or RMS (older age > 15 years, presence of metastatic disease, tumour volume > 100 mL or axial site involvement)	Melphalan + etoposide + carboplatin (n = 14); Cyclophosphamide + etoposide + carboplatin + dexamethasone (n = 7)	41 months	22y (15–35)	17 enrolled ESFT (14 proceeding to HDT)	3-year FFS: 50 % (P < 0.01) following HDT	Detailed – 1 TRD

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Table 1 (*continued*)

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Diaz 2010	Retrospective case series	Monocentric	Spain	High risk localised (tumour volume greater than 200 mL, inoperable tumour, or poor histological response), metastatic at diagnosis	BuMel	92 months	13yo (4–21)	47	PFS at median follow-up: 56 % ± 4 %	Detailed
Ladenstein 2010	Single arm trial (part of a larger RCT)	Multicenter	Austria	Primary disseminated disease	BuMel (n = 136); MelMel (n = 13); others (n = 20)	3.8 years	16.2yo (0.4–49)	281 enrolled (169 HDT)	3-year EFS: 27 % (SD 3 %) 3-year OS: 34 % (SD 4 %)	Detailed
Drabko 2011	Retrospective cohort study	Multicenter	Poland	Metastatic disease, localized and unresectable or poor histological response	BuMel (n = 32); TreoMel (n = 3)	54 months	13.2yo (1mo to 19yo)	35 (HDT)/ 26 (CC)	RFS at median follow-up: 66 % (HDT in HR patients) vs. 27 % (CC in HR) with p = 0.008OS at median follow-up: 71 % (HDT in HR) vs. 31 % (CC in HR) with p = 0.007	Minimal - TRM and secondary malignancies
Ferrari 2011	Retrospective cohort study	Multicenter	Italy	Non-metastatic primary	BuMel	64 months	15yo (3–40)	300	5-year EFS: 72 % [95 % CI 64–80 %, HDT] vs. 33 % [95 % CI 11–55 %, CC poor responder] vs. 75 % [95 % CI 68–82 %, CC good responder]	Detailed
Lopez 2011	Retrospective case series	Monocentric	Spain	HR at diagnosis: (1) patients with non-metastatic axial skeleton tumours; (2) patients with lung/ pleural metastasis, if CR at week 18; (3) patients with multicentric tumour or with BM metastasis if response ≥ 50 % at week 18	BuMel; MelEtop (n = 5); others	78 months	10yo (2–15)	27	2-year EFS: 74 % [95 % CI 52–96 %] 5-year EFS: 54 % [95 % CI 30–78 %] 2-year OS: 93 % [95 % CI 81–105 %]5-year OS: 73 % [95 % CI 51–95 %]	No specific toxicity information
Gaspar 2012	Retrospective cohort study	Multicenter	France	Localised disease. Risk group based on volume, clinical and histological response - IR large unresected	BuMel	8 years	12.6yo (0.5–28)	48 (HR receiving HDT)/ 46 (IR)/ 116 (SR)	5-year EFS: 48 % [95 % CI: 35–68 %, HR] vs. 54 % [95 % CI 40–68 %, IR] vs. 70 % [95 % CI	Basic

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Table 1 (*continued*)

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
				tumour > 100 mL or 5–30 % viable cells, HR viable cells > 30 % or < 50 % clinical response					61–77 %, SR]	
Loschi 2015	Single arm trial	Monocentric	France	Newly diagnosed metastatic ES, other than isolated pulmonary	Thiotepa + BuMel	9 years	Not stated	18	1-year EFS: 67 % 3-year EFS: 11 % 1-year OS: 78 %5-year OS: 22 %	Detailed
Whelan 2018	Randomized controlled trial	Multicenter	UK	HR localised	BuMel	7.8 years	17.1y (11mo to 44.7y)	118 (HDT)/ 122 (CC)	1-year EFS: 69 % [95 % CI 60.2–76.6 %] vs. 56.7 % [95 % CI 47.6–65.4 %] 8-year EFS: 60.7 % [95 % CI 51.1–69.6 %] vs. 47.1 % [95 % CI 37.7–56.8 %] 3-year OS: 78 % [95 % CI 69.6–84.5 %] vs. 72.2 % [95 % CI 63.3–79.6 %]8-year OS: 64.5 % [95 % CI 54.4–73.5 %] vs. 55.6 % [95 % CI 45.8–65.1]	Detailed
Dirksen 2019	Randomized controlled trial	Multicenter	Germany	Pulmonary/ pleural metastases in the absence of other distant metastases	BuMel	8.1 years	14.2y (1.0–47.8)	144 (HDT)/ 143 (CC)	3-year OS: 68.2 % (95 % CI, 60.0 % to 75.4 %) vs. 68.0 % (95 % CI, 59.7 % to 75.2 %) 3-year EFS: 56.6 % (95 % CI, 48.3 % to 64.6 %) vs. 50.6 % (95 % CI, 42.3 % to 58.9 %) 8-year OS: 55.3 % (95 % CI,46.1 % to 64.0 %) vs. 54.2 % (95 % CI, 45.3 % to 62.8 %) 8-year EFS: 52.9 % (95 % CI, 44.5 % to 61.2 %) vs. 43.1 % (95 % CI,	Basic

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remaining studies, 18 were Level III-2 and III-3 [17], and nearly half were Level IV as per the NHMRC Evidence Hierarchy (n = 19).

Ewing sarcoma

This systematic review identified 31 studies addressing the impact of HDT/ASCT in ES (Table 1-3). These included three randomised controlled trials, five single arm prospective trials and multiple retrospective cohort studies and case series predominantly from American and European cooperative clinical trials groups and sarcoma registries.

HDT/ASCT as part of first-line treatment in high-risk or poor prognosis Ewing sarcoma

Seventeen studies evaluated HDT/ASCT as part of first-line therapy in ES and provided data on survival outcomes (Table 1). These included the published results from three different arms of two European prospective randomised controlled clinical trials, Euro-E.W.I.N.G. 99 and EWING 2008 studies [10,18,19]. The observed impact of HDT/ASCT differed for the different arms of these trials, with only one study finding evidence for the utility of HDT [10].

Whelan et al. examined the outcome of 240 patients with high-risk localised disease and found improved EFS and OS with HDT/ASCT after VIDE backbone chemotherapy. VIDE was standard induction regimen in Europe before interval compressed VDC/IE chemotherapy was recognised as being more effective in the Euro-Ewing 2012 trial [22]. This study included patients enrolled in the 'R2Loc' arm of the Euro-E.W.I.N.G.99 or EWING-2008 studies [10] where all received six VIDE (vincristine/ifosfamide/doxorubicin/etoposide) induction courses and one VAI (vincristine/ actinomycin/ ifosfamide) consolidation course. High-risk disease was defined as disease with poor histological or radiological response to induction chemotherapy (residual viable cells $\geq$ 10 % or $<$ 50 % radiological reduction of the soft tissue disease component in small unresected tumours) or large tumour volume at diagnosis ($\geq$200 mL). In the R2Loc arm, high risk patients were randomised to receive a further seven courses of VAI or one course of high-dose BuMel (Busulfan-Melphalan) chemotherapy with ASCT. A significant benefit for HDT/ASCT was observed in EFS (HR of 0.64; 95 % CI 0.43–0.95; P = 0.026) and OS (HR 0.63; 95 % CI 0.41–0.95; P = 0.028). The 3-year EFS was 69.0 % (95 % CI, 60.2 %-76.6 %) for the HDT/ASCT arm vs 56.7 % (95 % CI, 47.6 %-65.4 %) for the VAI arm. The 8-year EFS was 60.7 % (95 % CI, 51.1 %-69.6 %) versus 47.1 % (95 % CI, 37.7 %-56.8 %) for the HDT, and VAI arms, respectively. The 3- and 8-year OS were, respectively, 78.0 % (95 % CI, 69.6 %-84.5 %) versus 72.2 % (95 % CI, 63.3 %-79.6 %) and 64.5 % (95 % CI, 54.4 %-73.5 %) versus 55.6 % (95 % CI, 45.8 %-65.1 %).

In patients with isolated pleural or pulmonary metastases at diagnosis ('R2Pulm' arm in Euro-E.W.I.N.G.99 and EWING-2008) the effect of BuMel HDT/ASCT (n = 144) was prospectively compared to standard VAI consolidation chemotherapy with whole-lung irradiation (WLI) (n = 143) by Dirksen et al. A numerical difference in EFS was observed with HDT; the EFS at 8 years was 52.9 % for the HDT/ASCT group versus 43.1 % for the VAI plus WLI group. However, the hazard ratio was non-significant (HR 0.79, 95 % CI 0.56–1.10, p = 0.16) and no significant OS benefit was observed (HR 1.00, 95 % CI 0.70–1.44; P = 0.99) [18]. Four patients (2.8 %) died as a result of HDT-related toxicity.

In the Euro-E.W.I.N.G.99 trial, 281 patients with primary disseminated multifocal ES were included in a non-randomised arm of the trial (this excluded patients with isolated pulmonary metastases enrolled in the 'R2pulm' arm) [23]. Of these 281 patients, 169 (60 %) received BuMel-HDT. The reported 3-year EFS and OS were respectively 27 % (95 % CI 21 %–33 %) and 34 % (95 % CI 26 %-42 %) for all 281 patients [23].

The incompatibility of BuMel HDT with radiation therapy to axial sites, due to lung toxicities observed with Busulfan, prompted the search for an alternative regimen. Treosulfan is a prodrug of a bifunctional alkylating agent. It is structurally related to busulfan and reported to have a low non-haematological toxicity [24]. Subsequently, in the Ewing 2008 R3 arm, 109 patients with primary disseminated ES were randomly assigned to either TreoMel HDT/ASCT (treosulfan-melphalan)

Table 1 (*continued*)

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
									34.9 % to 51.6 %)	
Koch 2022	Randomized controlled trial	Multicenter	Multiple countries	HR at diagnosis - metastatic to bone and/or other sites +/- pulmonary	TreoMel	3.3 years	15.8y (4.4–45.4)	55 (HDT)/ 54 (CC)	1-year EFS: 51.8 % [95 % CI 39.7–67.5 %] vs. 39.8 % [95 % CI 28.6–55.4] 3-year EFS: 20.9 % [95 % CI 11.5–37.9 %] vs. 19.2 % [95 % CI 10.8–34.4] 3-year OS: 43.4 % [95 % CI 30.7–61.3 %] vs. 37.4 % [95 % CI 25.5–54.7] 5-year OS: 26.8 % [95 % CI 14.8–48.6 %] vs. 33.6 % [95 % CI 21.8–51.9]	Basic

(n = 55) or no further treatment following consolidation chemotherapy (n = 54) [19]. Patients with pulmonary only metastases were again excluded. No significant difference in EFS (HR 0.72, 95 % CI 0.46–1.12, p = 0.37) or OS (HR 0.96 (95 % CI 0.58–1.58, P = 0.87)) was observed in the overall cohort, however a 3-year EFS benefit with HDT/ASCT was seen in children aged less than 14 years old (39.3 % vs 9 %, p = 0.016; HR 0.40 (0.19–0.87)(19). One HDT-related death was reported.

Of the remaining studies, five retrospective cohort studies, five case series and three prospective single arm studies (without a comparison arm) studied the use of HDT/ASCT in the first line. Interpretation of EFS

Table 2
Studies including refractory/relapsed Ewing sarcoma.

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Shankar 2003	Retrospective cohort study	Multicenter	UK	Relapsed disease	Melphalan +- TBI	Not stated	14yo (2–27)	7 (HDT) / 28 (combined modality)	Median OS: 49 vs. 14 monthsRR (death): 0.22 [95 % CI 0.08–0.62] vs. 0.46 [95 % CI 0.27–0.78]	No specific toxicity information
Rasper 2014	Retrospective cohort study	Multicenter	Germany	First relapse	TreoMel (n = 38); BuMel (n = 15); others (n = 20)	Not stated overall	CC 17.6yo, BuMel HDT 16.7yo, TreoMel HDT 17.6yo	53 (HDT) / 161 (CC)	1-year EFS: 87 % BuMel vs. 80 % TreoMel vs. 23 % CC 2-year EFS: 47 % BuMel (SD 0.13) vs. 44 % TreoMel (SD 0.09) vs. 10 % CC (SD 0.02) 5-year EFS: 20 % BuMel (SD 0.1) vs. 24 % TreoMel (SD 0.1) vs. 6 % CC (SD 0.02) 1-year OS: 93 % BuMel vs. 97 % TreoMel vs. 46 % CC 2-year OS: 53 % BuMel (SD 0.13) vs. 66 % TreoMel (SD 0.09) vs. 22 % CC (SD 0.03)5-year OS: 40 % BuMel (SD 0.13) vs. 42 % TreoMel (SD 0.11) vs. 10 % CC (SD 0.03)	Minimal, TRM and secondary malignancies only
Ferrari 2015	Retrospective cohort study	Multicenter	Italy	Relapsed disease	Ifosfamide +/- BuMel	Not stated	19yo (6–43)	80 (high-dose ifosfamide given to 50 patients, including 20 patients who received BuMel HDT, 30 patients other CC)	5-year PRS: 50 % [95 % CI 28–72 %, BuMel] vs. 12 % [95 % CI 2–25 %, ifosfamide only] vs. 5 % [95 % CI 4–14 %, other treatments]	Minimal, TRM only
Aykan 2022	Retrospective case series	Monocentric	Turkey	Primary refractory or recurrent	ICE	Not stated	26.85yo	20 (ES) / 4 (RMS)	Mean PFS: 2.7 months (SD 0.97) for ES / 3.47 months (SD 0.44) for RMS1-year OS: 44.8 % (SD 14.8 %) for ES vs. 75 % (SD 21.7 %) for RMS	Basic
Windsor 2022	Retrospective cohort study	Monocentric	UK	Primary refractory or recurrent	BuMel (n = 39); TreoMel (n = 14); other	233 months	18.3y (4.5–66.2)	64 (HDT) / 98 (CC)	Median PRS: 76 months (95 % CI 34.8–117.2) vs. 10.5 months (95 % 8.9–12.1), p < 0.0005 2-year PRS: 67.9 % (SD 5.9 %) vs. 20.5 % (SD 20.5 %)5-year PRS: 52.7 % (SD 6.5 %; 6 censored) vs. 2 % (SD 1.5 %)	No specific toxicity information

Table 3
Studies including both primary and refractory/relapsed Ewing sarcoma.

Study	Design	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Atra 1997	Single arm trial	Two centers	UK	Poor risk (metastatic n = 11, bulky n = 6, second complete remission n = 1)	BuMel	2 years	14.2yo (2.75–30)	18	Median OS: 3 years 9 months (if metastatic)Median EFS: 1 year 5 months (if metastatic)	Detailed
Laws 1999	Retrospective case series	Monocentric	Germany	Multifocal primary disease, relapsed disease	TBI + melphalan + etoposide	Not stated	Mean 18yo (10—–31)	25	EFS at time of study: 0.34 (SD 0.11)	Detailed
Al-Faris 2007	Retrospective cohort study	Monocentric	Canada	Metastatic/multifocal disease at diagnosis (n = 26), relapsed disease (n = 19)	Etoposide + cyclophosphamide + melphalan (n = 17); other (n = 3)	6 years (HDT)/ 2 years (CC)	HDT 12.42yo (3.7–16.9), CC 11.75yo (1.75–16.1)	20 (HDT)/ 25 (CC)	3-year OS: 59 vs. 34 %, p = 0.06 3-year EFS: 39 % vs. 32 %, p = 0.08	Basic
Gardner 2008	Retrospective case series	Multicenter	USA	Primary or relapsed disease	TBI +/- second agent n = 59; Mel +/- second agent (non-Busulfan) n = 31; others	57 months	18yo	109	5-year PFS in patients with localized and metastatic disease at diagnosis: 49 % [95 % CI 30–69 %]and 34 % [95 % CI 22–47 %] respectively 5-year PFS in patients with localized disease at recurrence: 14 % [95 % CI 3–30 %]	Minimal, TRM only
Rosenthal 2008	Single arm trial	Monocentric	USA	Metastatic bulky disease at the time of diagnosis or recurrent disease	BuMel (n = 11); busulfan + carboplatin (n = 9); others	2.4 years	16.24yo (6.48–29.93)	20	1-year EFS: 45 % [95 % CI 23–65 %] 3-year EFS: 45 % [95 % CI 25–70 %] 1-year OS: 60 % [95 % CI 36–78 %]3-year OS: 45 % CI [95 % CI 22–69 %]	Detailed
Avramova 2011	Retrospective cohort study	Monocentric	Bulgaria	Bulky (n = 21), metastatic (n = 23), early relapse (n = 13)	BuMel (n = 11); others	39.3—–50.7 months	12.8yo (3–30)	20 (CC 1985–1997)/ 22 (CC 1997–2010)/ 15 (HDT)	DFS at median follow-up: 15 % (CC 1985–1997) vs. 19 % (CC 1997–2010) vs. 29 % (HDT)OS at median follow-up: 25 % (CC 1985–1997) vs. 27 % (CC 1997–2010) vs. 23 % (HDT)	Basic
Serlo 2013	Retrospective cohort study	Multicenter	Finland	Bone and soft tissue ESFT at any stage	Not stated	7.0 years	17.8yo	76	5-year EFS: 67 % vs. 59 %, p = 0.817 5-year DSS (localised): 67 % vs. 71 %, p = 0.6625-year DSS (metastatic): 74 % vs. 0 %, p < 0.001	No specific toxicity information
Jahnukainen 2015	Retrospective cohort study	Monocentric	Finland	Metastatic disease or localized tumours > 200 mL at diagnosis, poor histological response to induction or non-radical surgery, recurrent disease	Thiotepa +/- etoposide +/- carboplatin; melphalan + TBI	11.8 years	10yo (1 to 16)	24	10-year OS: 0.73 (SD 0.16, transplanted in 1CR) vs. 0.9 (SD 0.09)	Basic
Pawlowska 2021	Retrospective case series	Monocentric	USA	Primary metastatic disease, relapsed disease	Topotecan + BuMel; others	7.4 years	14yo (2–28)	47	1-year DFS: 43 % [95 % CI 28–56 %] 15-year DFS: 37 % [95 % CI 24–51 %] 3-year OS: 46 % [95 % CI 31–60 %] 15-year OS: 42 % [95 % CI 28–56 %]	Detailed

Abbreviations: BuMel – busulfan melphalan; CC – conventional chemotherapy; CI – confidence interval; CR – complete response; DFS – disease-free survival; DSS – disease-specific survival; EFS – event-free survival; HDT – high-dose chemotherapy; HR – high-risk; IR – intermediate risk; PFS – progression-free survival; PR – partial response; PRS -post-relapse survival; OS – overall survival; SR – standard risk; RMS – rhabdomyosarcoma; SD – standard deviation; TreoMel – treosulfan melphalan; TBI – total body irradiation; TRM – treatment-related mortality; yo – year old.

Table 4
Studies for RMS – first line, relapse and both.

Study	Design	First-line / relapse	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Carli 1999	Non-randomised trial	First-line	Multicentre	Italy	Primary metastatic	Melphalan +- other	42.8 months	7.7y (3mo-18y)	52 (HDT) / 44 (CC)	3-year EFS: 29.7 vs. 19.2 %, p = 0.33-year OS: 40 % vs. 27.7 %, p = 0.2	Basic – TRD 1 HDT, 1 CC
Matsubara 2003	Retrospective case series	Both	Single centre	Japan	(1) Clinical group III or IV disease at the primary diagnosis or (2) local relapse or distant metastasis in patient with clinical group I or II disease	Hi-MEC (n = 10); others	Not stated overall	8.5y (2–22)	22	5-year DFS: 36 %5-year OS: 45 %	Basic – 0 TRD
Carli 2004	Retrospective cohort study	First-line	Multicentre	Italy	Primary metastatic	Melphalan	8 years	8.6y (3.2mo-18.8y)	95 (HDT) / 79 (CC)	5-year OS: 36 % [95 % CI 23–49 %] vs. 27 % [95 % CI 14–41 %]5-year EFS: 29 % [95 % CI 16–41 %] vs. 23 % [95 % CI 11–36 %]	Basic – 6 TRD
Williams 2004	Retrospective cohort study	First-line	Single centre	Canada	Primary metastatic	Etoposide + cyclophosphamide +/- melphalan	5.5 years	Range < 18y	4 (HDT) / 13 (CC)	3-year OS: 100 % [95 % CI 33–107 %) vs. 15 % [95 % CI −4–35 %], p = 0.03 3-year FFS: 75 % (95 % CI 33–107 %) vs. 15 % (95 % CI −4–35 %), p = 0.04	Basic, no TRM reported
Bisogno 2009	Single arm trial	First-line	Not stated	Italy	Primary metastatic	Sequential HDT combinations – thiotepa/melphalan, cyclophosphamide/ thiotepa, melphalan	5 years	9.4y (0.9mo-20.9y)	70	1-year PFS: 35.3 % [95 % CI 24.3–46.5 %]1-year OS: 43.6 % [95 % CI 39.5–53.6 %]	Detailed – 3 TRD
Stiff 2010	Retrospective case series	Both	Multicentre	USA	All stages	Varied	78 months	14y (3–40)	62	1-year PFS: 36 % [95 % CI 24–48 %] 3-year PFS: 29 % [95 % CI 18–41 %] 5-year PFS: 29 % [95 % CI 18–41 %] 1-year OS: 56 % [95 % CI 43–68 %] 3-year OS: 39 % [95 % CI 28–52 %]	TRM only – 3 TRD

(*continued on next page*)

and OS is difficult due to the heterogeneity of inclusion criteria in terms of staging, types of small round blue cell tumours without availability of advanced genomics testing, and differences in backbone chemotherapy regimens used (Table 1) [14, 25–36]. Nine additional studies included patients treated with HDT/ASCT upfront as well as at relapse (Table 3) [37–45].

Amongst these studies, a couple of relatively large comparative studies have reported improvements in outcomes in patients receiving HDT/ASCT versus conventional chemotherapy. Drabko et al. retrospectively evaluated 102 patients (age 1–19 years) with metastatic, unresectable or poorly responsive ES and primitive neuroectodermal tumours (PNET) and reported a significant improvement in 2-year relapse-free survival (RFS) and OS with HDT/ASCT compared to conventional chemotherapy (RFS 66 % vs 27 % respectively, $p < 0.01$ and OS 71 % vs 31 %, $p < 0.01$) [26]. Serlo et al. retrospectively analysed 76 patients with ESFT receiving various unspecified HDT/ASCT or conventional chemotherapy consolidation regimens [45]. In 15 patients with metastatic disease, where 9 received HDT, a significant increase in 5-year disease-specific survival (DSS) post HDT/ASCT (74 % vs 0 %, $p < 0.001$) was observed. In patients with localised disease, no significant improvement in 5-year DSS was seen with HDT/ASCT (67 % with HDT/ASCT vs 71 %, $p = 0.662$), however a non-significant improvement in disease-free survival (DFS) was observed (67 % with HDT/ASCT vs 59 %, $p = 0.817$). Other studies did not show a significant difference in EFS or OS for patients with primary metastatic or relapsed ES [35,37], or localised disease with poor radiological or histological response treated with HDT/ASCT [28].

Retrospective cohort studies by Gaspar et al. and Jahnukainen et al. report lower 5-year and 10-year OS rates for patients who underwent HDT/ASCT compared to conventional chemotherapy however the efficacy of HDT/ASCT cannot be determined due to the non-randomised, risk-group stratified treatment protocols designs [29,41]. Other non-comparative studies are small, enrolling between 18 and 57 patients who underwent HDT/ASCT (Tables 1 and 3). Most of these studies are retrospective, largely heterogeneous in nature and their evidence is weak towards the benefit of using HDT/ASCT as part of first-line therapy [1,2,4,7,9,16,18,19,22,23,27,31,34,40,46–48].

Prognostic factors in ES first line studies of HDT/ASCT

The prognostic impact of the following variables were investigated across multiple studies: clinical remission prior to HDT, age and histological response to induction chemotherapy. Incomplete response to chemotherapy at time of HDT was associated with lower EFS or OS in patients with newly diagnosed ES in multiple studies [23,25–27,43]. Patients with primary multifocal disseminated ES with stable disease (SD) or progressive disease [49] at the time of HDT achieved a lower 3-year EFS rate than patients with partial remission (PR) and patients in CR (3-year EFS: SD/PD 24 % (95 % CI 10 %-38 %), PR 32 % (95 % CI 22 %-42 %), CR 57 % (95 % CI 37 %-77 %) [23].

In univariate analysis, younger patients appear to benefit more from HDT/ASCT than older patients. In Whelan et al., patients younger than 25 years old treated with HDT/ASCT had a better outcome ($p = 0.12$) [10]. Similarly, patients with primary disseminated multifocal ES younger than 14 years old had a better outcome following TreoMel HDT/ASCT (HR 0.40, 95 % CI 0.19–0.87) [19]. Pawlowska et al. identified older age (>18 years of age) to confer a higher risk of relapse regardless of remission status at the time of HDT [43].

An association of histological response to induction chemotherapy with post HDT outcome is unclear. Whelan et al., reported patients with an 'intermediate poor' (10 to 29 % viable cells) histological response to initial therapy benefited more from HDT than those with a very poor (≥30 % viable cells) response (interaction test, $p = 0.06$) [10]. Laurence et al. reported a significant survival benefit in patients with ESFT who had a good histological response (5 year OS 77 % vs 44 % in those with poor pathological response with ≥ 10 % viable cells, $p = 0.03$ Breslow test) [30].

HDT/ASCT for relapsed Ewing sarcoma

Fourteen studies evaluated patients with relapsed or refractory Ewing sarcoma [37–45,47,48,50–52]. Of these 14 studies, 5 considered HDT/ASCT for relapsed and refractory ES only (Table 2) and nine in both first line and relapsed/refractory settings (Table 3).

Four retrospective cohort studies specific to relapsed or refractory ES reported a significant improvement in outcomes with melphalan-based HDT/ASCT versus conventional chemotherapy, albeit with small numbers [47,48,51,52]. In Ferrari et al., 5-year post-relapse survival was 50 % (95 % CI 28 %-72 %) in 20 patients who responded to high-dose ifosfamide and proceeded to receive BuMel HDT; 12 % (95 % CI 2 %-25 %) in 30 patients treated with high-dose ifosfamide chemotherapy alone due to prior HDT or inadequate response to ifosfamide; and 5 % (95 % CI 4 %-14 %) in 30 patients treated with other conventional treatment regimens [51].

Rasper et al. specifically reported the outcome of patients with relapsed disease who achieved CR or PR following 4 to 6 cycles of salvage chemotherapy. Some patients then received BuMel or TreoMel HDT/ASCT (n = 7) as consolidation whereas others received no further therapy (n = 34) [47]. The 2-year and 5-year EFS were 44 % (95 % CI 26 %-62 %) and 22 % (95 % CI 4 %-40 %, $p = 0.93$), for patients receiving HDT/ASCT versus 31 % (95 % CI 15 %-47 %) and 18 % (95 % CI 2 %-34 %) for those who did not receive further therapy. The 2-year and 5-year OS was 59 % (95 % CI 41–77 %) and 41 % (95 % CI 21 %-61 %, $p = 0.13$) versus 45 % (95 % CI 27 %-63 %) and 25 % (95 % CI 9 %-41 %) respectively.

A small retrospective cohort study by Shankar et al. described a

Table 4 (*continued*)

Study	Design	First-line / relapse	Setting	Country	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Kim 2012	Retrospective cohort study	First-line	Single centre	Korea	Primary high risk (Group III/IV patients at diagnosis by IRS staging, Stage III or IV disease by TNM staging)	Ifosfamide + carboplatin + etoposide	7.3 years	5y (6 m-15y)	13 (HDT) / 24 (CC)	5-year OS: 32 % [95 % CI 21–44 %] 5-year EFS: 41.3 % (SD 17.8 %) vs. 16.7 % (SD 7.6 %) with $p = 0.023$	Basic – TRD 0 HDT, 1 CC

Table 5
Studies including RMS amongst other sarcomas.

Study	Design	First-line/ relapse	Setting	Country	Sarcoma types	Sarcoma classifiers	High-dose chemotherapy agents	Median follow-up	Median age (range)	Number of patients	Survival outcomes	Toxicity information
Boulad 1998	Single arm trial	First-line	Single centre	USA	RMS, extraosseous EWS, undifferentiated sarcoma	Primary metastatic disease or stage II/III disease at unfavourable sites	Melphalan + etoposide	62 months	14.8y (1.1 to 23).	26 (19 HDT)	2-year PFS: 53 % [95 % CI 33–73 %]2-year OS: 56 % [95 % CI 36–76 %]	Detailed – 0 TRD
Hosoi 2007	Retrospective cohort study	First-line	Multicentre	Japan	RMS, undifferentiated sarcoma	Primary intermediate risk and high-risk patients underwent HDT	HiMEC; TEPA/LPAM	4.3 years	5y (0–20)	63 (HDT)/67 (CC)	5-year OS (high-risk): 58.2 % (HDT) vs. 18.4 % (CC)5-year OS (intermediate): 61.6 % iHDT) vs. 54.5 % (CC)	No specific toxicity information
Yamada 2007	Single arm trial	First-line	Single centre	Japan	RMS, ESFT	Primary high-risk tumours	Melphalan + etoposide + carboplatin (n = 14); Cyclophosphamide + etoposide + carboplatin + dexamethasone (n = 7)	41 months	22y (15–35)	8 enrolled RMS (7 proceeding to HDT)	3-year FFS: 0 % following HDT	Detailed – 1 TRD
Klingebiel 2008	Non-randomised trial	First-line	Multicentre	Germany	RMS, other soft tissue sarcomas	Primary metastatic disease	HDT1 (cyclophosphamide and thiotepa) + HDT2 (melphalan + etoposide)	57.4 months	Range < 22y	45 (HDT)/ 51 (maintenance)	5-year OS: 0.27 (SD 0.13) vs. 0.52 (SD 0.14) with p = 0.03	TRM only – TRD 1 HDT, 0 CC
Aykan 2022	Retrospective case series	Relapse	Single centre	Turkey	Small round cell tumours	Primary refractory or recurrent	ICE	Not stated	26.85y	20 (ES)/ 4 (RMS)	Mean PFS: 2.7 months (SD 0.97) for ES / 3.47 months (SD 0.44) for RMS1-year OS: 44.8 % (SD 14.8 %) for ES vs. 75 % (SD 21.7 %) for RMS	Basic – 1 TRD

Abbreviations: CC– conventional chemotherapy, ESFT – Ewing sarcoma family of tumour, FFS – failure-free survival, HDT – high-dose chemotherapy, OS – overall survival, PFS – progression-free survival, RMS - rhabdomyosarcoma, TRD – treatment-related death, TRM – treatment related mortality, SD – standard deviation.

median survival of 49 months for seven patients who received HDT, including 4 in CR and 2 in PR at the time of HDT, compared to 14 months for 28 patients continuing a conventional regimen, including 3 in CR and 11 in PR [52]. However, all patient in the HDT/ASCT group with the exception of one have subsequently relapsed.

Windsor et al. reported a 2-year and 5-year post-relapse survival of 67.9 % (95 % CI 56.3 %-79.5 %) and 52.7 % (95 % CI 40.0 %-65.4 %) respectively in 64 patients who underwent HDT, compared to 20.5 % (95 % CI 19.7 %-60.7 %) and 2 % (95 % CI 0 %-4.9 %) respectively in 98 patients continuing conventional chemotherapy [48]. Of the 64 patients receiving HDT, response to induction chemotherapy prior to HDT was available for 55; responses included 21 (38 %) CR, 28 (51 %) PR, 4 (7 %) SD and 2 (3 %) PD. The remission status of patients not receiving HDT was not reported.

The remaining studies do not compare outcomes with conventional chemotherapy and are heterogeneous, as shown in Table 3.

Prognostic factors in ES relapsed/refractory ES studies of HDT/ASCT

Gardner et al. reported poorer survival in patients with refractory disease immediately prior to HDT [40]. In both the Rasper and Pawlowska studies, the time from diagnosis to relapse was an important prognostic factor in multivariate analysis [43,47]. In Rasper et al., early relapse (<2 years from diagnosis) was an unfavourable prognostic factor (HR 4.76, EFS, $p < 0.01$) and (HR 3.70, OS, $p < 0.01$)(47), and similarly, late relapse was a protective factor (HR 0.36, 95 % CI 0.14 % to 0.92 %; $P = 0.032$) in Pawlowska et al. [43]. Finally, in the Rasper study, patients in CR/PR had more risk of events when not receiving HDT, with a HR of 2.90 (EFS, $P < 0.01$) and 2.61 (OS, $P = 0.01$).

Toxicities, treatment-related mortality, and secondary malignancies in ES

Twenty-six studies reported on treatment related deaths, six studies reported on secondary malignancies [10,18,19,26,30,47], and five studies provided a comparison of toxicities in each treatment group [10,18,19,28,35].

Increased rates of high grade toxicities were observed with HDT. Whelan et al. reported that in patients who received BuMel chemotherapy, 'severe' haematological (grade 4 as per National Cancer Institute Common Terminology Criteria for Adverse Events [53]), 'severe' gastro-intestinal or respiratory tract toxicities (grade 3 or above), and fever or infection (grade 3 and above) were observed in 98.8.%, 71.2 % and 32.5 % of patients respectively [10]. In Koch et al., in patients who received TreoMel-HDT, deterioration in general condition, severe haematological, infection and gut toxicities were recorded in 26 %, 98 %, 39 % and 48 % of patients respectively [19]. In the five studies where a comparison of toxicities in each treatment group was provided, all concluded severe acute toxicities occurred more frequently in the HDT/ASCT arm. Koch et al. documented more frequent infections, gastrointestinal (GI) and renal toxicities ($P < 0.05$) [19], as well as more frequent grade 4 haematological toxicities and grade 3 + non-haematological toxicities. Dirksen et al. reported that 'significantly more

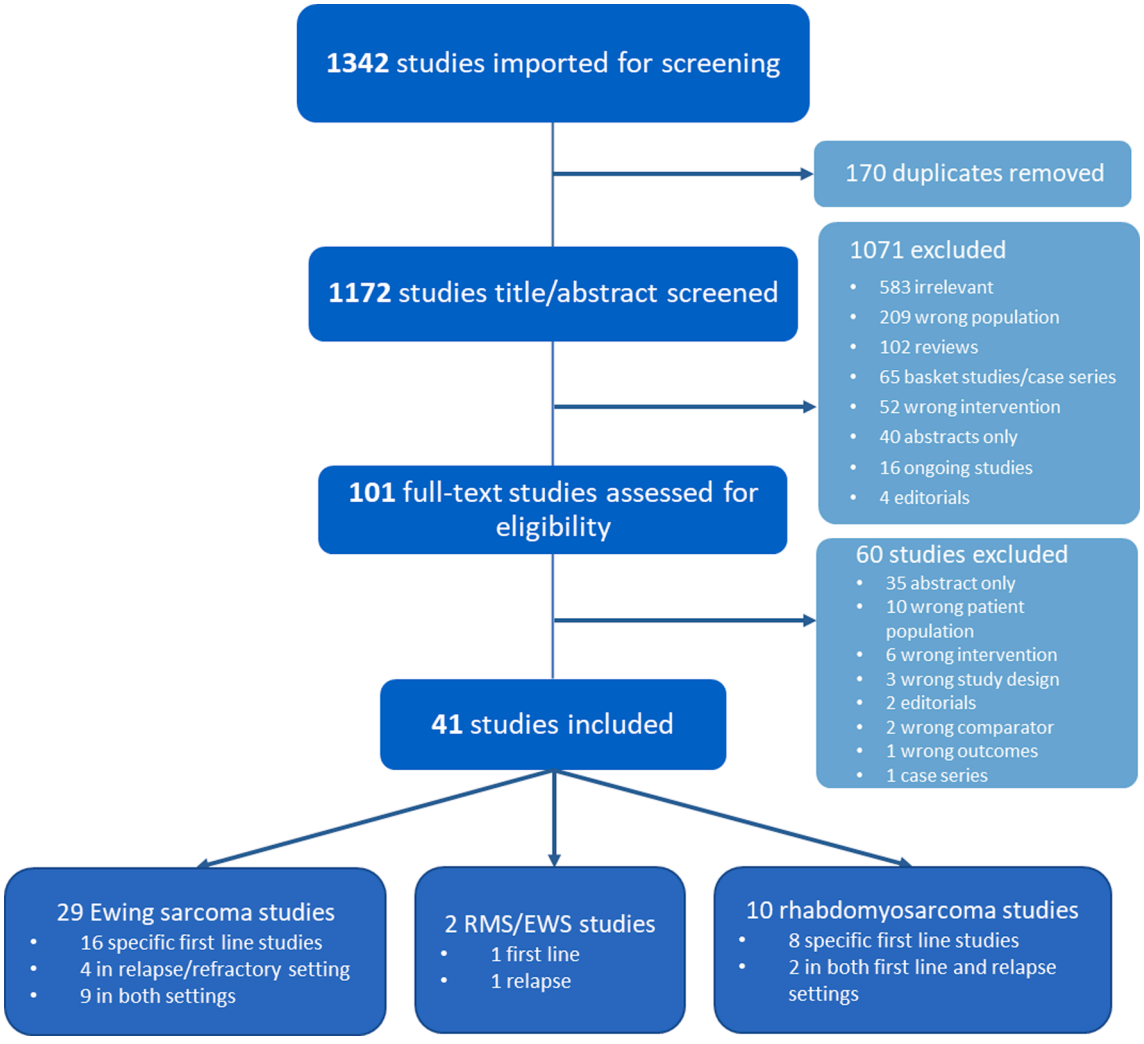

Fig. 1. PRISMA flow diagram of the systematic review.

patients experienced severe acute toxicities', in particular, GI, liver and haematological toxicities, infections, as well as other toxicities such as pain, fatigue, fever, chills and malaise ($P < 0.05$) [18]. Comparable toxicities were observed in the study by Whelan et al. ($P < 0.05$) and Paulussen et al. [10,35]. Ferrari et al. noted that haematological toxicities were higher in the HDT/ASCT group, reporting 3 % of patients to be thrombocytopenic following VAC-IVA-IE versus 95 % following HDT [28]. Although data of late effects was not collected, Dirksen et al. discuss infertility, in both male and female patients, as an additional side effect anticipated with HDT/ASCT that is not expected in female patients after standard therapy and WLI [18].

Treatment-related deaths with HDT/ASCT were reported in 25 of the 26 studies that commented on treatment-related toxicities. The three randomised controlled trials found mortality rates to be under 3 % in the HDT group. Whelan et al. [10] and Dirksen et al. [18] reported three (3/118 enrolled patients) and four (4/144 enrolled patient) deaths in the BuMel-arm respectively; Koch et al. reported no treatment-related deaths secondary to TreoMel-HDT [19]. However, treatment-related mortality (TRM) rates varied significantly by study given the significant heterogeneity in patient population, myeloablative chemotherapy regimen and study protocols used.

Secondary malignancies were reported in six studies. Drabko et al. reported three secondary malignancies, all in the group without HDT/ASCT [26]. Rasper et al. reported four deaths from secondary malignancies (acute myeloid leukaemia and melanoma), without providing details on allocated treatment [47]. Laurence et al. did not find any secondary malignancies in the surviving patients at a median follow-up of 7.1 years [30]. Three other studies showed the number of secondary malignancies to be similar across the HDT/ASCT and conventional chemotherapy arms [10,18,19].

Rhabdomyosarcoma

Systematic review identified 12 studies addressing the impact of HDT/ASCT in RMS. Two non-randomised prospective studies were available with studies largely consisting of retrospective data from American and European sarcoma registries.

HDT/ASCT as part of first-line treatment in rhabdomyosarcoma

Seven studies reported on the use of HDT/ASCT as first-line treatment specifically in RMS [12,28,54–59] (Table 4). The outcomes of two prospective non-randomised cooperative studies in Europe, MMT4-89 and MMT4-91, of paediatric patients with metastatic stage IV RMS were analysed twice, in 1999 and 2004 respectively [12,55]. Both studies report that HDT, given as consolidation after complete remission, did not significantly improve EFS or OS. In 1999, the reported 3-year EFS was 40 % for HDT/ASCT versus 27.7 % for conventional chemotherapy ($P = 0.2$) and 3-year OS was 29.7 % for HDT/ASCT ($n = 52$) versus 19.2 % for conventional chemotherapy ($n = 44$, $P = 0.3$) in 96 patients with primary metastatic RMS [55]. The 2004 study yielded similar results, documenting a 5-year EFS of 29 % (95 % CI 16 %-41 %) for HDT/ASCT versus 23 % (95 % CI 11 %-36 %) for conventional chemotherapy and a 5-year OS of 36 % (95 % CI 23 %-49 %) for HDT/ASCT ($n = 94$) versus 27 % (95 % CI 14 %-41 %) for conventional chemotherapy ($n = 79$) in 174 enrolled patients with primary metastatic RMS [12].

Kim et al. retrospectively reviewed outcomes of 37 patients (aged 6 month to 15 years) with high-risk RMS (defined as stage III or IV disease), of which 13 underwent HDT with ifosfamide/carboplatin/etoposide and ASCT, and 24 patients had conventional chemotherapy only. A significant improvement in 5-year EFS was noted in patients who received HDT/ASCT (41.3 %, 95 % CI 23.5 %-59.1 %) versus 16.7 %, 95 % CI 9.1 %-24.3 %) ($p = 0.023$), however overall survival rates were not reported. In that study, the 5-year EFS was higher in patients with RMS who achieved CR or very good PR at the time of ASCT (50.0 %, 95 % CI 29.6 %-70.4 % vs 37.5 %, 95 % CI 8.9 %-66.1 % for other patients) [56].

The remaining RMS studies contribute with a lower level of evidence: one study included a small sample size of only 17 patients [59] and three studies did not compare outcomes with conventional chemotherapy [54,57,58].

Four heterogenous studies that grouped RMS and RMS-like tumours provided survival results in first-line treatment (Table 5). Hosoi et al. retrospectively reviewed 331 patients that were classified as per the Intergroup RMS Study V (IRS-V) risk group classification. A significant 5-year OS benefit for HDT/ASCT was seen in patients in the high-risk group, defined as having primary metastatic disease at diagnosis or undifferentiated sarcoma (58.2 % vs 18.4 %; HR 0.38, 95 % CI 0.17–0.88, in 42 patients of which 22 received HDT). This was not seen in the intermediate-risk subgroup B tumours (88 patients, of which 41 received HDT) (5-year OS of 61.6 % vs 54.5 %; HR 0.82, 95 % CI 0.38–1.77) [60]. In this study, the majority of patients (301 of 331) were determined to have a histological diagnosis of RMS. Further histopathological subtyping identified 67 and 117 patients with ARMS or ERMS respectively. No significant difference in OS rates was seen in patients with ARMS and ERMS but notably, the FOX01 fusion status was known in only 10 % of cases. In a prospective, non-randomised study of 96 children with primary metastatic soft tissue sarcoma (predominantly confirmed RMS) who received standard induction chemotherapy, 45 patients received HDT/ASCT as consolidation at the discretion of the treating physician, and were found to have a lower OS compared to those who received an oral maintenance regimen (OS 0.27 vs 0.52, $p = 0.03$) [20]. The study included 45, 29, 14 and eight patients with ARM, ERMS, 'RMS-like' and 'non-RMS-like' patients respectively. The remaining two studies had no comparison group [36,46].

HDT/ASCT for relapsed/refractory RMS disease

Only three studies included patients with relapsed/refractory disease. These were all retrospective case series of small number of patients ($n = 4$, 22 and 62 respectively) and included patients receiving HDT/ASCT as part of first-line treatment [50,57,58](Table 4). It is therefore not possible to draw any conclusion from these studies.

Toxicities, treatment-related mortality and secondary malignancies in RMS

Eleven studies provided information on treatment toxicity; however, toxicities were generally not reported comprehensively and only two studies provided a comparison of toxicities in each treatment group [20,56]. As expected, severe haematological toxicities were reported with HDT [12,56,57]. Carli et al. cited myelosuppression as the most frequent adverse effect of HDT with 83 %, 60 %, and 45 % of patients developing CTCAE grade 3 or 4 neutropenia, thrombocytopenia, and anaemia, respectively [12]. In the two studies that compared toxicities between conventional chemotherapy and HDT/ASCT groups, haematologic complications were observed in both groups without statistical differences, although multiple grade 3 and 4 toxicities in the setting of HDT were recorded in supplementary material [20,56].

Treatment related deaths were recorded in 10 of the 11 RMS studies. The rate was 0 to 4 % (Table 4&5) [12,20,36,46,50,54–58]. The largest study reported six toxic deaths amongst 174 patients, including four from sepsis and two from anthracycline-related cardiotoxicity, although no details were given on their treatment group [12]. An earlier study by the same first author reported one death in both the HDT/ASCT and conventional chemotherapy groups [55]. Kim et al. reported no deaths in the HDT/ASCT group and one death in the conventional chemotherapy group [56]. Klingebiel et al. reported one death in the HDT/ASCT arm and no deaths in the conventional chemotherapy group [20]. Only two studies reported on secondary malignancies. Yamada et al. reported two patients who developed secondary malignancies following HDT, and Matsubara et al. observed no secondary malignancy over a

median follow up time of 99 months [36,57].

Discussion

In this systematic review of HDT/ASCT in ES and RMS, findings and level of evidence varied for the two tumour types. For ES, 31 studies were available and included prospective international multicentre randomised studies. For RMS, no randomised evidence was available, and the evidence was limited to 12, largely retrospective, studies.

There was randomised prospective evidence of benefit of HDT/ASCT in ES with high-risk localised disease, treated with the now superseded VIDE chemotherapy backbone, and retrospective evidence (four studies) for improved survival outcomes with HDT/ASCT for relapsed or refractory ES. No proven survival benefit with HDT/ASCT was found for the treatment of primary metastatic ES nor primary localised, metastatic or relapsed RMS.

For RMS, this systematic review identified a lack of evidence in this sarcoma subtype with only twelve studies addressing the impact of HDT/ASCT. Most studies included patients with high risk and/or metastatic RMS, and minimal evidence was available for HDT/ASCT in relapsed and refractory disease. There were no prospective randomised studies and available studies are largely based on retrospective data from American and European sarcoma registries. Most studies reported OS and toxicities of HDT/ASCT were not reported comprehensively. The highest-level evidence encompassed two large prospective non-randomised cooperative studies of HDT/ASCT in patients with primary metastatic disease and found no improvement in OS or EFS [12,55]. Two studies, by Hosoi et al. and Kim et al., report improved OS in patients with high-risk disease, however these were retrospective analyses of very small size (22 and 13 patients received HDT/ASCT in Hosoi et al. and Kim et al. respectively). Due to a lack of high-quality studies assessing HDT/ASCT in relapsed RMS, it is not possible to infer the utility of HDT/ASCT in treating relapsed disease.

Based on this systematic review, the ANZSA guidelines working party concludes that HDT/ASCT has no proven benefit in high risk and metastatic primary RMS, or relapsed/refractory RMS. The authors recommend that patients with RMS should not undergo HDT/ASCT outside of a clinical trial setting (Supplementary Table 3).

In ES, the treatment of primary disease, melphalan-based HDT/ASCT as first line therapy, may convey an OS and EFS benefit to patients with primary localised high-risk ES [10]. Survival benefits are not confirmed for patients with metastatic disease at initial diagnosis [18,19]. The benefit, however, was demonstrated where the initial chemotherapy backbone used was VIDE. Interval compressed chemotherapy with vincristine, doxorubicin, cyclophosphamide (VDC) alternating with ifosfamide/etoposide (IE) every 2 weeks, however, has been proven to be superior to VIDE and is the recommended first line chemotherapy regimen in ES [22]. This was shown in randomized controlled trial, EE2012, comparing the use of these two induction regimens, which were standard of care in the US (VDC/IE) and in Europe (VIDE) [22]. Significant improvements in survival outcomes were demonstrated; 3-year EFS was 61 % in the VIDE group versus 67 % in the VDC/IE group (HR 0·71, 95 % CI 0·55–0·92) and 3-year OS was 74 % in the VIDE group versus 82 % in the VDC/IE group (HR 0·62, 95 % CI 0·46–0·85). This clinical benefit was also demonstrated across all clinical groups. In this study, only six (2 %) of patients received Bu/Mel consolidation following VDC/IE [22]. For patients with localised ES treated with the recognised standard 2-weekly VDC/IE regimen, the role of HDT/ASCT is therefore unknown. Clinical trials testing HDT/ASCT consolidation with this regimen are needed to determine if it remains beneficial. Considering the evidence available to date and the comparable outcomes published with VDC/IE with a vincristine and cyclophosphamide consolidation [22] in comparison to VIDE followed by HDT/ASCT consolidation [10,18,19], th guidelines working group would not recommend the use of HDT/ASCT in the treatment of primary ES. The current international INTER-EWING-1 clinical trial (NCT05830084) allows for HDT/ASCT consolidation after VDC/IE induction chemotherapy and thus may provide further information regarding its benefit and toxicity. The evidence, however, will likely be limited, as this is not a randomised intervention, but rather is based on physician preference.

For treatment of relapsed/refractory ES, there is retrospective evidence that HDT/ASCT may be associated with improved survival in selected patients. The evidence appears greatest for patients who achieve CR or PR before HDT, and patients under the age of 14, as well as those who relapse two years or more, after diagnosis. Noting the poor prognosis of ES patients with relapsed disease and based on our systematic review, the recommendation of the ANZSA guidelines working group is that in selected patients with relapsed ES, HDT/ASCT can be considered. Patients who achieve PR of their relapsed disease with second line chemotherapy appear to be the best candidates. Such patients should be managed in specialised sarcoma centres, and patients and their guardians should be guided judiciously through the potential but uncertain benefits of HDT, where toxicities are often severe in grade and include a higher risk of treatment related death (Supplementary Table 3).

Regarding treatment regimens, a wide range of agents were utilised for conditioning prior to ASCT in the studies included in this review. Interestingly, choice of chemotherapeutic agents did not differ significantly by histopathological diagnosis. Rather, this variance is likely owing to the heterogeneity in study location, clinician experience, study timing and treatment setting. The most common regimen seen was BuMel (n = 15) followed by TreoMel and other melphalan-based combinations. Traditionally, busulfan has been utilised for conditioning before pediatric ASCT owing to its efficacy and known safety profile. However, busulfan is known to cause liver, skin and lung toxicity, haemorrhagic cystitis, sinusoidal obstruction syndrome, and long-term gonadal abnormalities [24,61]. Additionally, busulfan has high interpatient variability and its excretion is age-dependent and non-linear [61]. Furthermore, the incompatibility of BuMel HDT with radiation therapy to axial sites, due to lung toxicities, led to the use of a different regimen in sarcoma. As mentioned, Treosulfan, a prodrug of a bifunctional alkylating agent, has shown to confer less haematological toxicity, although there is limited data available comparing the two agents in pediatric patients [24]. It also has a more stable pharmacokinetic profile with minimal interpatient variation [61]. There are no studies comparing conditioning regimen prior to ASCT in sarcoma.

A limitation of this review is the large volume of retrospective data where the choice of treatment group was left to the discretion of the treating physician. This is likely to have introduced significant bias based on confounding factors including disease severity, treatment setting and patient preference.

Moving forward, prospective randomised clinical trials are required to clarify the survival benefit (or lack thereof) of HDT/ASCT in RMS, and in ES after VDC/IE interval compressed chemotherapy. The patient populations where evidence is greatest and may support initiation of randomised trials include those with primary localised high-risk ES and those with relapsed ES that have responded to re-induction chemotherapy. To our knowledge, there are currently no active trials specifically addressing the role of HDT/ASCT in ES or RMS. As discussed above, in currently open international trials including patients with ES, HDT/ASCT is optional and left to the investigator's preference. The focus of these recent trials is to investigate the potential added benefit of targeted agents to standard chemotherapy, such as regorafenib in metastatic ES (REGO-Ewing phase Ib substudy of the international INTER-EWING-1 clinical trial (NCT05830084) [62]) and relapsed RMS [FaR-RMS, NCT04625907 [63]), and lenvatinib in relapsed ES (rEECur clinical trial [64]). FaR-RMS and INTER-EWING-1 also study the possible benefit of 6–12 months of maintenance chemotherapy at the end of standard first-line chemotherapy for high-risk patients, and 12–24 months of maintenance therapy for very high-risk patients with RMS. With this change of strategy, evidence to robustly determine the role of HDT, in EWS and RMS, might never be fully obtained.

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Ashika Ramamurthy: Data curation, Writing – original draft, Writing – review & editing. **Elizabeth A Connolly:** Writing – review & editing. **Jasmine Mar:** Project administration, Software, Writing – review & editing. **Jeremy Lewin:** Writing – review & editing. **Vivek A Bhadri:** Writing – review & editing. **Marianne B Phillips:** Writing – review & editing. **Mark Winstanley:** Writing – review & editing. **Lisa M Orme:** Writing – review & editing. **Peter Grimison:** Writing – review & editing. **Joanna Connor:** Writing – review & editing. **Smaro Lazarakis:** Methodology, Software. **Angela M Hong:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Natacha Omer:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Julie Cayrol:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

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Appendix A. Supplementary data

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