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# High-dose thiotepa-based chemotherapy with autologous stem cell support in elderly patients with primary central nervous system lymphoma - a European retrospective study

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1 **Abstract**

2 In this retrospective multicentre study, we investigated the outcome of elderly PCNSL  
3 patients ( $\geq 65$  years) who underwent HDT-ASCT at eleven centres between 2003  
4 and 2016. Endpoints included remission, progression free survival, overall survival  
5 and treatment-related mortality.

6 We identified 52 patients (median age 68.5 years, median KPS before HDT-ASCT  
7 80%) who all underwent thiotepa-based HDT-ASCT. Fifteen patients (28.8%)  
8 received HDT-ASCT as first-line treatment and 37 (71.2%) received it as second or  
9 subsequent line. Remission status before HDT-ASCT was: complete remission (CR)  
10 34.6%, partial remission (PR) 51.9%, stable disease 3.8%, and progressive disease  
11 9.6%. Following completion of HDT-ASCT, 36 patients (69.2%) achieved CR (21.2%  
12 first line setting, 48.1% second or subsequent line setting) and 9 (17.3%) PR (5.8%  
13 first line setting, 11.5% second or subsequent line setting). With a median follow up  
14 of 22 months after HDT-ASCT, median PFS and OS were reached after 51.1 and  
15 122.3 months, respectively. 2-year PFS and OS rates were 62.0% and 70.8%,  
16 respectively. We observed two HDT-ASCT associated deaths (3.8%).

17 In selected elderly PCNSL patients, HDT-ASCT, using thiotepa-based conditioning  
18 regimes, is feasible and effective. Further prospective and comparative studies are  
19 warranted to further evaluate the role of HDT-ASCT in elderly PCNSL patients.

20

21

## 22 **Introduction**

23 Primary central nervous system lymphoma (PCNSL) is an aggressive Non-Hodgkin  
24 Lymphoma, typically diffuse large B cell lymphoma (DLBCL), which exclusively involves the  
25 central nervous system at diagnosis. It accounts for 3% to 4% of all primary brain tumours  
26 and 4% to 6% of extra-nodal lymphomas (1). The incidence of PCNSL in immunocompetent  
27 patients has been steadily increasing over the last 30 years (2, 3). However, notwithstanding  
28 progress over the last decade with improved immunochemotherapy approaches, PCNSL  
29 remains a challenging disease.

30 Patients older than 65 years account for 50% of all PCNSL cases (4). Although some elderly  
31 patients may tolerate intensive systemic chemotherapy, they typically experience an inferior  
32 prognosis as compared to younger patients with PCNSL. Moreover, elderly patients are  
33 vulnerable to iatrogenic toxicity, especially neurotoxicity following whole brain radiation  
34 therapy (WBRT) (4); thus they represent a unique treatment subgroup (5, 6). An US registry  
35 study of 579 elderly patients diagnosed with PCNSL in the 1990s described a median  
36 survival of only 7 months and that WBRT alone was the most common treatment modality  
37 (46%) (7). Even with modern conventional chemotherapy protocols, most patients will  
38 experience a short progression free survival (PFS) (<12months) and die from disease (8, 9).  
39 For younger patients, thiotepa-containing high-dose chemotherapy followed by autologous  
40 stem cell transplantation (HDT-ASCT) has been shown to be feasible and effective in both  
41 newly diagnosed and relapsed patients with PCNSL (10-15). Due to toxicity and tolerability  
42 concerns, this intensive CNS-directed treatment has typically been restricted to patients  
43 younger than 65 years of age. However, age alone may not be the appropriate criterion to  
44 select patients for this effective treatment approach.

45 We undertook this retrospective, international study to investigate outcome after HDT-ASCT  
46 in elderly PCNSL ( $\geq 65$  years) from eleven centres with experienced physicians, who have  
47 been treating PCNSL patients and performing clinical trials in PCNSL for many years.

## 48 **Methods**

### 49 *Patient selection criteria and data collection*

50 Eligibility criteria for this retrospective multicentre analysis were i) age  $\geq$  65 years at the time  
51 of HDT-ASCT; ii) histologically-proven PCNSL (at first diagnosis, no repeat biopsy required  
52 at relapse) without systemic lymphoma manifestation at any time; iii) no evidence of  
53 immunodeficiency; iv) completed thiotepa-based HDT-ASCT. All centres screened their  
54 databases for PCNSL patients  $\geq$  65 years, excluding patients not treated with HDT-ASCT.  
55 Data from all study-eligible patients of the eleven cooperating centres were collected using a  
56 pre-specified, anonymised case report form, including: patient and tumour characteristics at  
57 baseline, treatment, transplantation specific data, main reported toxicities, objective  
58 response, site and date of relapse or progression, and survival. Data were checked by the  
59 coordinating investigators for consistency and, if necessary, queries resolved with sites  
60 before entering data into the central database. All patients provided informed consent for the  
61 documentation of anonymised clinical data and the use for scientific publication. The ethics  
62 committee of Freiburg University approved the study protocol.

63

### 64 *Statistical analysis*

65 The principal outcomes of interest were remission status before and after HDT-ASCT  
66 (complete remission [CR], partial remission [PR], stable disease [SD], progressive disease  
67 [PD]) as reported by the respective centres, PFS (defined as time from HDT-ASCT to  
68 progression, relapse or death; whichever occurred first) and overall survival (OS, defined as  
69 time from HDT-ASCT to death due to any cause). PFS and OS were estimated using the  
70 Kaplan-Meier method including 95% confidence interval (CIs). We additionally stratified  
71 response and survival outcomes by line of treatment in which HDT-ASCT was undertaken  
72 (first line versus second or subsequent line), and by remission status before HDT-ASCT. The  
73 follow-up time was estimated using the inverse Kaplan-Meier method. All analyses are  
74 considered exploratory in nature and were conducted using the software package R version  
75 3.2.4 ([www.r-project.org](http://www.r-project.org)).

## 76 **Results**

### 77 *Patient characteristics*

78 Fifty-two eligible PCNSL patients who were treated with HDT-ASCT between 2004 and 2016  
79 were included. Patients' baseline characteristics at time of diagnosis and before HDT-ASCT  
80 are summarized in **Table 1**. Forty-eight patients had parenchymal disease manifestation  
81 (with or without involvement of deep brain lesions) and four patients had primary vitreoretinal  
82 lymphoma without parenchymal manifestations. Prior to HDT-ASCT, most patients had a  
83 good clinical performance status (median Karnofsky performance status 80%, range 30% to  
84 100%). Eighteen of 52 patients (34.6%) were in CR, 27 of 52 (51.9%) in PR, 2 of 52 (3.8%)  
85 had SD, and 5 of 52 (9.6%) had experienced PD following induction treatment.

86 The majority of patients had previously received a HD-MTX-based protocol (98.1%) as first  
87 line therapy with 38 of 52 patients (73.1%) having received MTX-AraC-based  
88 polychemotherapy, 12 of 52 patients (23.1%) MTX-based polychemotherapy, one patient  
89 MTX-monotherapy and another patient MTX-free polychemotherapy. Rituximab was added  
90 in 33 of 52 patients (63.5%). Most of the 37 patients with relapsed or refractory disease after  
91 first-line therapy received a polychemotherapy of carboplatin, ifosfamide and etoposide with  
92 or without rituximab or a AraC - and thiotepa-based salvage regimen. None of the patients  
93 had received WBRT before HDT-ASCT; one patient received WBRT as salvage therapy after  
94 HDT-ASCT. Five patients received intrathecal therapy with liposomal cytarabine. None of the  
95 patients received intraventricular therapy.

96

### 97 *Conditioning regimen and ASCT-specific data*

98 The majority of patients was conditioned with TT 10-20 mg/kg + carmustine 320-400 mg/m<sup>2</sup>  
99 (61.5%). Remaining patients received TT 10-20 mg/kg + busulfan 3.2-6.4 mg/kg (13.5%), TT  
100 250-750 mg/m<sup>2</sup> + busulfan 2.4–8.0 mg/kg + cyclophosphamide 60-120 mg/kg (13.5%) or TT  
101 10 mg/kg as single agent (11.5%). Rituximab was additionally given in 2 patients (3.8%). The  
102 median number of reinfused CD34+ hematopoietic stem cells was 5.29 x 10<sup>6</sup>/Kg (range 2.24  
103 to 35). Median time to neutrophil engraftment was 10 days (range 6 to 34). We observed two

104 (3.8%) treatment related deaths within 15 days after HDT-ASCT. One patient suffered from  
105 sudden death attributed to an acute cardiovascular event whilst the second patient died from  
106 infectious complications.

107

#### 108 *Treatment response and survival*

109 **Table 2** summarizes the response status after HDT-ASCT, stratified by line of therapy and  
110 remission status prior to HDT-ASCT. Following HDT-ASCT, 45 of 52 patients (86.5%)  
111 achieved an objective response (36 CR and 7 PR). One patient (1.9%) experienced SD  
112 whilst 5 (9.6%) had PD one month after HDT-ASCT.

113 Of the 15 patients undergoing HDT-ASCT as first-line treatment, 14 patients (93%) achieved  
114 an objective response (11 CR and 1 PR). Of the 37 patients undergoing HDT-ASCT as  
115 second or subsequent line of treatment 31 patients (83.8%) achieved an objective response.

116 One of five patients with PD before HDT-ASCT achieved ongoing CR (PFS 50 months)  
117 without further consolidating treatment. Three of the other four patients achieved partial  
118 remission and one patient had stable disease, although all four subsequently experienced  
119 PD.

120 After a median follow up of 22.1 months, 36 of 52 patients (69.2%) were still alive with 31  
121 free of disease progression after HDT-ASCT. For one patient who experienced PD, the exact  
122 date of death was not known, therefore the patient was censored at the date of progression  
123 for the OS analysis. Apart from the two patients suffering from treatment related deaths  
124 thirteen patients died from progressive disease whereas one patient was lost of follow up  
125 after experiencing progressive disease with the exact cause of death being unknown.

126 For the entire cohort, median PFS and OS were reached after 51.1 and 122.3 months,  
127 respectively. 2-year PFS and OS probabilities were 62.0% (95% CI 48.4% to 79.6%) and  
128 70.8% (95% CI 58.3% to 85.9%), respectively (**Figure 1 and 2**). For the patients undergoing  
129 HDT-ASCT as first-line treatment 2-year PFS and OS probabilities were 80% (95% CI 51.6%  
130 to 100%) and 80.0% (95% CI 51.6% to 100%), respectively (**Figure 3**). For the patients  
131 undergoing HDT-ASCT at second or subsequent line of treatment 2-year PFS and OS

132 probabilities were 54.0% (95% CI 39.1% to 74.4%) and 65.6% (95% CI 51.5% to 83.6%)  
133 respectively (**Figure 4**). The PFS and OS rates by remission status before HDT-ASCT are  
134 shown in **online figures 1** and **2** suggesting that patients with chemosensitive disease have  
135 a better prognosis. Because of the limited patient numbers and events, we did not conduct  
136 any statistical testing.

137

138



139 **Discussion**

140 We herein describe outcomes of elderly PCNSL patients who underwent thiotepa-based  
141 HDT-ASCT. The overall response rate after HDT-ASCT was 86.5%, with 2-year PFS and OS  
142 rates of 62.0% and 70.8%, respectively. Two patients (3.8%) died early of HDT-ASCT-  
143 related causes.

144 *Strengths and limitations*

145 To the best of our knowledge, this is the first cohort reporting data on elderly patients who  
146 underwent HDT-ASCT for PCNSL. Considering the rarity of the disease, the cohort size is  
147 relatively large. Moreover, the dataset has a very low number of missing values and all  
148 patients underwent relatively homogenous conditioning with thiotepa-based HDT-ASCT  
149 protocols.

150 We recognise that our study has limitations, the first of which is inherent to any transplant  
151 analysis; patients were only included if they underwent HDT-ASCT and we are not able to  
152 report outcomes on an intent-to-treat basis. Thus, one can only use these outcome data to  
153 inform patients about prognosis following HDT-ASCT. Second, we do not have detailed  
154 information on relevant co-morbidities that would allow calculation of specific indices that  
155 may help to standardise selection of older patients for HDT-ASCT.

156 *Comparison to other studies*

157 WBRT is still employed as a common treatment modality in some countries (7) for elderly  
158 PCNSL patients, even though such patients are particularly vulnerable to iatrogenic toxicity,  
159 especially neuro-cognitive dysfunction following WBRT (4). Addition of WBRT after  
160 methotrexate-based chemotherapy is known to increase the risk of treatment-related  
161 neurotoxicity (16). Importantly, in our cohort, none of the patients received consolidating  
162 WBRT after HDT-ASCT. Although neurocognitive function was not formally assessed in our  
163 cohort, the merits of avoiding WBRT in older PCNSL patients is absolutely clear, particularly  
164 given these promising outcomes following HDT-ASCT.

165 Based on a recent systematic review (9), a limited number of prospective multicentre studies  
166 focusing on elderly PCNSL patients have been reported (8, 17-21). Most of the studies

167 included HD-MTX in combination with partner chemotherapy agents, but to-date no standard  
168 protocol has been defined. Acknowledging the limitations of inter-trial comparison, the best  
169 reported response rate was 79% but the corresponding 1-year PFS was only 36% (8). With  
170 an overall response rate of 86.5% and a 2-year-PFS of 62% the outcome of our reported  
171 population compares favourably with all other trials conducted in this unique subgroup of  
172 PCNSL patients. This is even more significant as only less than one third of the present  
173 cohort underwent HDT-ASCT in CR. Remarkably, even some patients with chemotherapy-  
174 refractory disease achieved sustained objective responses after HDT-ASCT although we  
175 acknowledge inherent selection bias within our cohort, likely to be related to favourable  
176 performance status and limited co-morbidities.

177 Although experience with HDT-ASCT in PCNSL is limited to prospective non-randomised  
178 studies in consolidation of first line therapy or for relapsed patients < 65 years, the results are  
179 encouraging; particularly when TT-containing conditioning regimens are used (10-12, 19,  
180 22). In a multi-centre retrospective analysis investigating patients with a median age of 52.4  
181 years undergoing HDT-ASCT as salvage therapy, 5-year survival rates of patients with  
182 chemosensitive relapse was 62% (13). In another large retrospective analysis investigating  
183 patients with a median age of 54 years undergoing HDT-ASCT as first line treatment, the  
184 reported 2- and 5-year survival rates were 82% and 79%, respectively. Notably, of the  
185 reported patients with PD before HDT-ASCT, 7/20 achieved ongoing CR without further  
186 treatment suggesting efficacy of HDT-ASCT even in disease refractory to conventionally  
187 dosed chemotherapy (23). The thus far published studies on ASCT as first-line treatment or  
188 at relapse are summarized in **Table 3**. Acknowledging the limitations of inter-trial  
189 comparisons, survival rates of the herein reported elderly population seem to be comparable  
190 to those of younger patients.

191 Patients with newly diagnosed PCNSL, aged between 65 and 70 years with ECOG  
192 performance status 0-2 have been included in the international, randomised, phase II  
193 IELSG32 trial (24), but evidence from prospective clinical trials specifically designed for  
194 elderly patients are still lacking.

195 All patients in our cohort received thiotepa-based regimens incorporating a total thiotepa  
196 dose of 10-20 mg/kg. In an ongoing German pilot study investigating feasibility of HDT-ASCT  
197 in elderly patients, the conditioning regimen comprises busulfan 3.2 mg/kg and thiotepa 10  
198 mg/kg (half of the dose routinely administered to younger patients) (DRKS-ID 00008900).  
199 Importantly, even for younger patient cohorts, randomised comparisons of different  
200 myeloablative combinations and doses have not been conducted; for elderly PCNSL  
201 patients, no such data is available.

202 For systemic diffuse large B-cell lymphoma (DLBCL), the current role of HDT-ASCT is  
203 restricted to relapsed patients responding to salvage therapy. Notably, the majority of HDT-  
204 ASCT studies in this context include younger patients with a median age of 54 years (25).  
205 Notwithstanding increasing clinical experience of undertaking HDT-ASCT for older patients  
206 with systemic DLBCL, there remains no clear standard for the selection of, or conditioning  
207 for, elderly patients undergoing HDT-ASCT.

208 Few data on feasibility and efficacy of HDT-ASCT in elderly patients are available in multiple  
209 myeloma (MM), lymphoma and acute leukaemia (26-28). The reported non relapse mortality  
210 rates in lymphoma patients older than 70 years who underwent HDT-ASCT differ strongly  
211 from 5.2% up to 19% (29-31). In our cohort, only two patients (3.8%) died from treatment  
212 related mortality, both within 15 days after HDT-ASCT due to a cardiovascular event and  
213 infectious complications.

214 The definition of an elderly patient with regard to therapeutic stratification is unclear;  
215 determined by multiple patient- and disease-related parameters. Thus, 'elderly' patients  
216 comprise a markedly heterogeneous group and it is unclear how to optimally define the frailty  
217 profile in this context. Comorbidity risk scoring, assessment of instrumental activities of daily  
218 living, and comprehensive geriatric assessments are likely to be important tools to define  
219 treatment-related mortality and overall treatment risk (32-35). To-date, treatment decisions  
220 have been largely based on chronological age and performance status. Although  
221 standardized assessment scores, especially for cancer patients, are available (36), these are  
222 infrequently used because of their complexity. Recently, a score for the quantitation of frailty

223 in designing future clinical MM trials was proposed (37). There is a clear need for a simple  
224 and validated tool to inform treatment decisions in elderly PCNSL.

#### 225 *Conclusions*

226 In selected elderly PCNSL patients, HDT-ASCT, using thiotepa-based conditioning regimens,  
227 is an effective and safe treatment if conducted at experienced centers, both in first-line and  
228 second or subsequent line of treatment. A pilot study investigating feasibility and efficacy of  
229 HDT-SCT in PCNSL patients > 65 years is currently recruiting (DRKS-ID 00008900).  
230 Prospective trials are needed to better define eligibility for this approach and to further  
231 improve therapeutic approaches in this unique and challenging subgroup of patients.

232

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235 centres.

236

#### 237 **Conflict of Interest**

238 The authors declare no conflict of interest.

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<b>Patient characteristics</b>	<b>HDT applied in first line N=15</b>	<b>HDT applied in second/subsequent line N=37</b>	<b>Total N=52</b>
Age at HDT-ASCT median (range)	70 (66, 75)	67 (65, 77)	68.5 (65, 77)
Sex			
female	7 (46.7)	17 (46)	24 (46.2)
male	8 (53.3)	20 (54)	28 (53.8)
KPS at diagnosis (median range)	65 (30, 90)	80 (40, 100)	70 (30, 100)
LDH			
elevated	8 (53.3)	10 (27)	18 (34.6)
not elevated	6 (40)	18 (48.7)	24 (46.2)
unknown	1 (6.7)	9 (24.3)	10 (19.2)
Deep brain structures involved			
yes	10 (66.7)	22 (59.5)	32 (61.5)
no	5 (33.3)	15 (40.5)	20 (38.5)
Ocular involvement			
yes	0 (0)	8 (21.6)	8 (15.4)
no	14 (93.3)	21 (56.8)	35 (67.3)
unknown	1 (6.7)	8 (21.6)	9 (17.3)
Leptomeningeal involvement			
yes		5 (13.5)	5 (9.6)
no	5 (33.3)	20 (54.1)	25 (67.6)
unknown	10 (66.7)	12 (32.4)	22 (42.3)
Histology			
Aggressive B-NHL	15 (100)	34 (91.9)	49 (94.2)
T-NHL	0 (0)	3 (8.1)	3 (5.8)
HDT-ASCT applied in			
1st line	15 (100)		15 (28.8)
2nd line		32 (86.5)	32 (61.5)
3rd line		5 (13.5)	5 (9.6)
KPS before HDT-ASCT median (IQR)	70 (70, 80)	80 (70, 90)	80 (70, 90)
Remission before HDT-ASCT			
CR	4 (26.7)	14 (37.8)	18 (34.6)
PR	11 (73.3)	16 (43.3)	27 (51.9)
SD	0 (0)	2 (5.4)	2 (3.8)
PD	0 (0)	5 (13.5)	5 (9.6)

**Table 1:** Patients' characteristics. Numbers are frequencies (percentage) unless specified otherwise. Remission status according to IPCG Response criteria

Abbreviations: IQR, interquartile range; KPS, Karnofsky Performance Status; Serum LDH, serum lactate dehydrogenase level, HDT-ASCT, high-dose chemotherapy followed by autologous stem cell transplantation; CR, complete remission, PR, partial remission, SD, stable disease, PD, progressive disease; IPCG, International PCNSL Collaborative Group

		Remission status before HDT-ASCT (1st line setting)				Remission status before HDT-ASCT (2nd or later line setting)			
		CR n=4	PR n=11	SD n=0	PD n=0	CR n=14	PR n=16	SD n=2	PD n=5
Remission status after HDT- ASCT	CR	4	7	0	0	12	11	1	1
	PR	0	3	0	0	0	3	0	3
	SD	0	0	0	0	0	0	0	1
	PD	0	1	0	0	1	2	1	0
	not applicable	0	0	0	0	1	0	0	0

**Table 2:** Remission status stratified by line of treatment and remission status before HDT-ASCT. In the first line setting, 3/3 patients with PR after HDT-ASCT only had minimal contrast abnormality in brain imaging after HDT-ASCT likely in terms of reactive post-therapy lesions and remained in confirmed complete remission for > 6 months after HDT-ASCT without any additional therapy. In the second or later line setting, only 1/6 patient with PR after HDT-ASCT remained in confirmed remission > 6 months after HDT-ASCT without any additional therapy.

Abbreviations: HDT-ASCT, high dose chemotherapy followed by autologous stem cell transplantation;

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease

<i>N° of patients</i>	<i>Trial design</i>	<i>median age (range)</i>	<i>HD-ASCT setting</i>	<i>Induction regimen</i>	<i>Conditioning regimen</i>	<i>WBRT</i>	<i>Follow-up (median)</i>	<i>OS</i>	<i>TRM</i>	<i>Reference</i>
33	prospective	57 (23-67)	1st line	R-MPV	Bu/TT/Cy	no	45	3 y: 81%	12%	(12)
30	prospective	54 (27-64)	1st line	HD-MTX+AraC/TT	BCNU/TT	yes	63	5 y: 69%	3%	(10)
28	prospective	53 (25-71)	1st line	HD-MTX+AraC	BEAM	no	28	2 y: 55%	4%	(38)
25	prospective	51 (21-60)	1st line	MBVP + IFO/AraC	BEAM	yes	34	4 y: 64%	4%	(39)
23	prospective	55 (18-69)	1st line	HD-MTX	Bu/TT	only if no CR	15	2 y: 48%	13%	(40)
13	prospective	56 (35-65)	1st line	MPV+AraC	LEED	only if no CR	44	3 y: 76%	0%	(41)
13	prospective	54 (38-67)	1st line	HD-MTX + AraC/TT	BCNU/TT	only if no CR	72	5 y: 77%	0%	(11) (42)
11	prospective	52 (33-65)	1st line	HD-MTX + AraC	BUCYE	only if no CR	25	2 y: 89%	0%	(43)
6	prospective	53 (30-66)	1st line	MBVP + IFO/AraC	BEAM	yes	41	2 y: 40%	0%	(44)
105	retrospective	54 (23-70)	1st line	mostly MTX-based polychemotherapy	mostly BCNU/TT	partly	47	5y: 79%	3%	(23)
21	retrospective	56 (34-69)	1st line	MPV + AraC	Bu/TT/Cy	no	60	5 y: 44%	24%	(45)
45	prospective	57 (19-72)	rel/ref	ICE or HD-MTX	Bu/TT	no	53	5 y: 40%	5%	(46)
43	prospective	52 (23-65)	rel/ref	AraC /VP16	Bu/TT/Cy	no	36	2 y: 45%	12%	(14)
22	prospective	53 (27-64)	rel/ref	AraC/VP16	Bu/TT/Cy	no	41	3 y: 64%	4%	(47)
79	retrospective	52 (23-67)	rel/ref	mostly AraC/VP16	TT/Bu/Cy	yes	56	5 y: 51%	8%	(13)
7	retrospective	58 (41-65)	rel/ref	unknown	TT/Bu/Cy	yes	34	not reached	0%	(48)

**Table 3:** Compendium of publications on HDT-ASCT in PCNSL

Abbreviations: HDT-ASCT, high dose chemotherapy followed by autologous stem cell transplantation; WBRT, whole brain radiation therapy; OS, overall survival; TRM, treatment related mortality; MPV, methotrexate, procarbazine, vincristine; HD-MTX, high-dose methotrexate; AraC, cytarabine; TT, thiotepa; MBVP, methotrexate, carmustine, etoposide, methyprednisolone; ifo, ifosfamide; ICE, ifosfamide, carboplatin, etoposide; VP16, etoposide; Bu, busulfan; BCNU, carmustine; BEAM, carmustine, etoposide, cytarabine, melphalan, LEED, cyclophosphamide, etoposide, melphalan, dexamethasone; BuCy, busulfan, cyclophosphamide; Cy, cyclophosphamide

Figure 1

PFS entire cohort

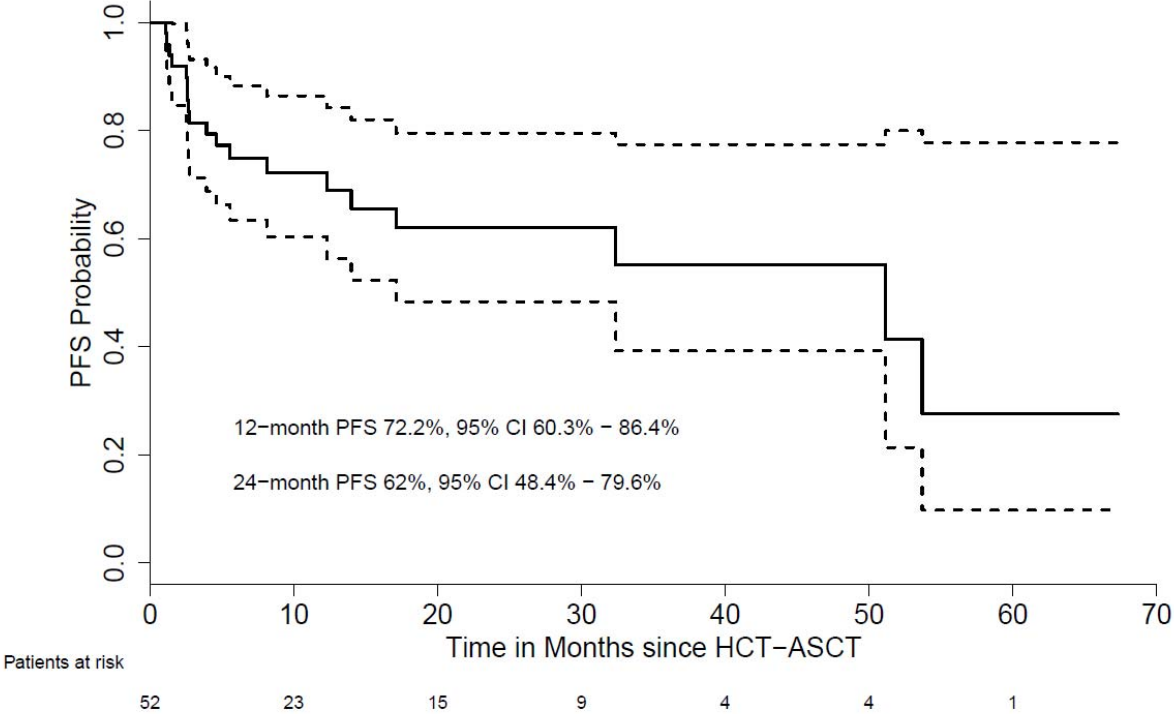


Figure 2

OS entire cohort

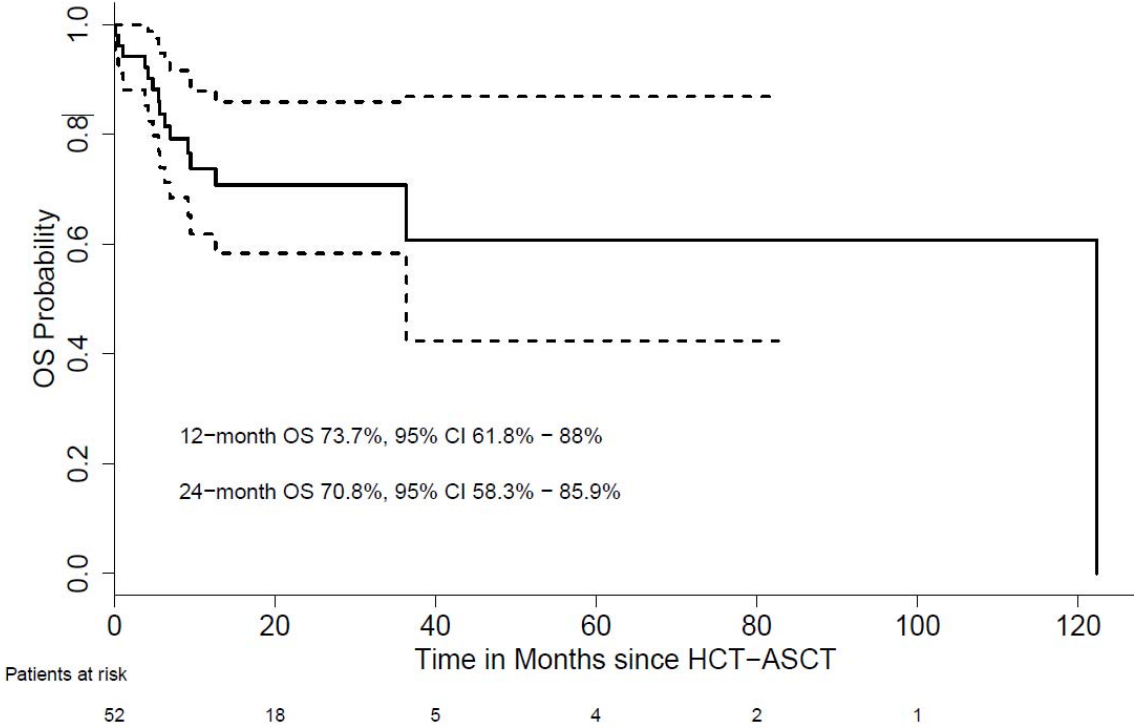
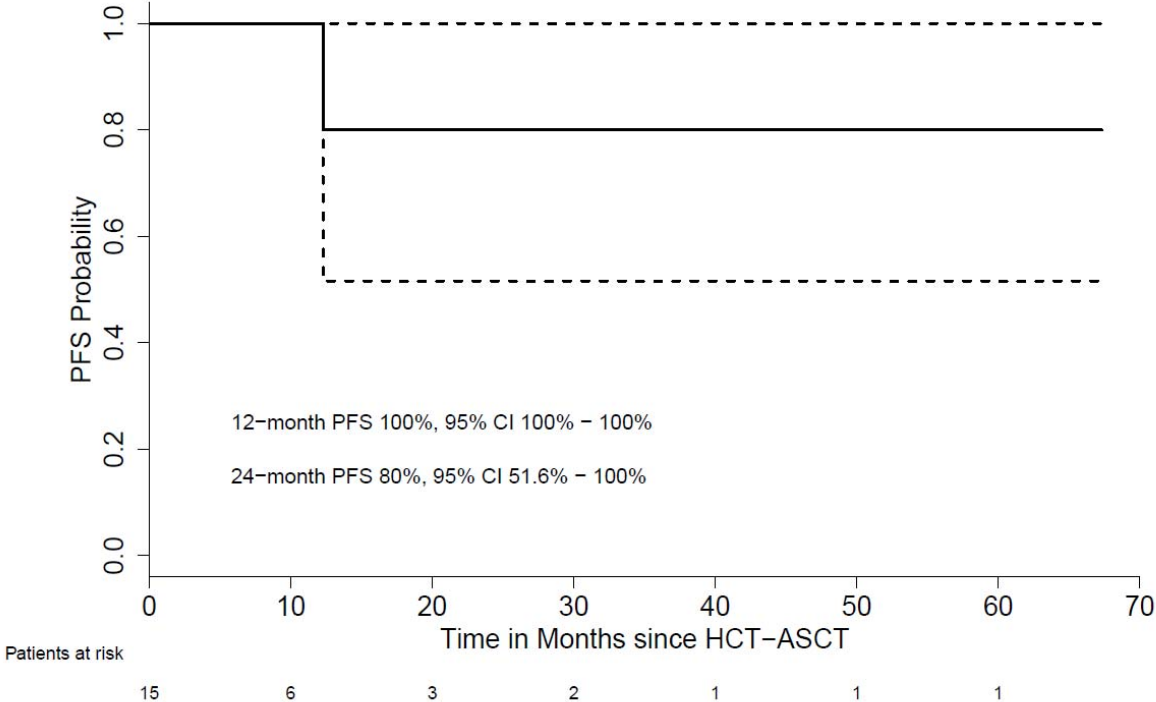


Figure 3

### PFS in patients with HCT-ASCT at 1st line



### OS in patients with HCT-ASCT at 1st line

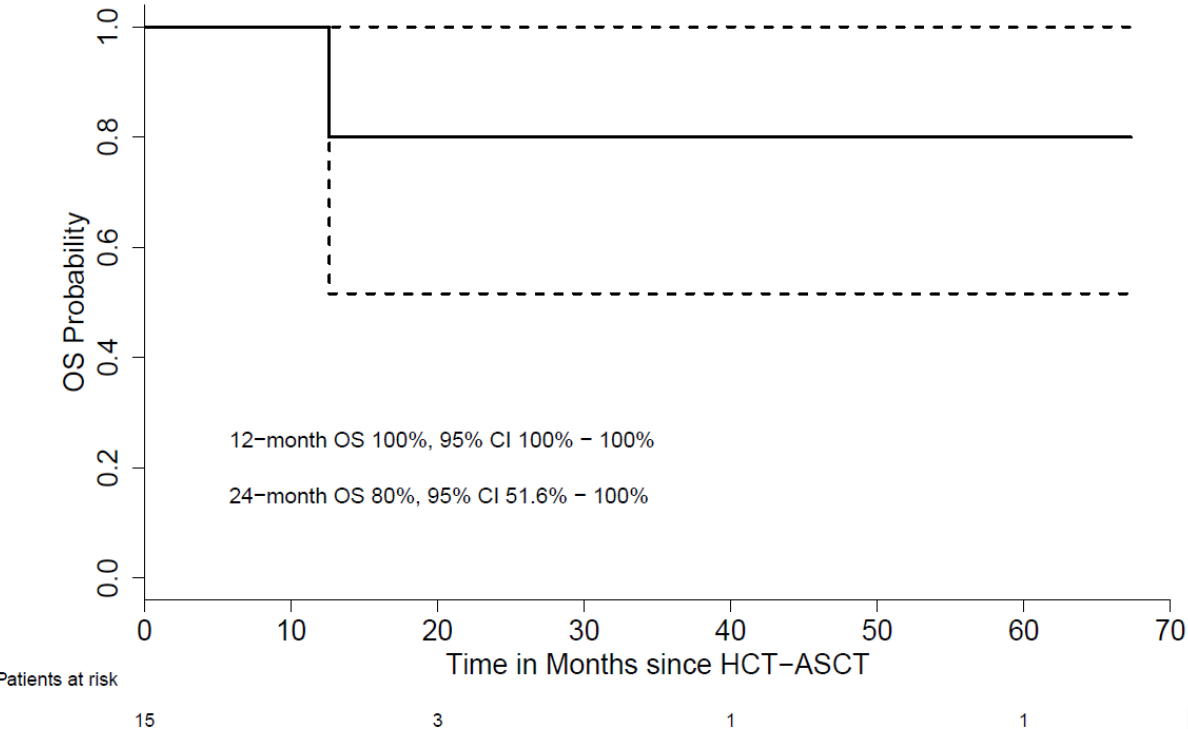
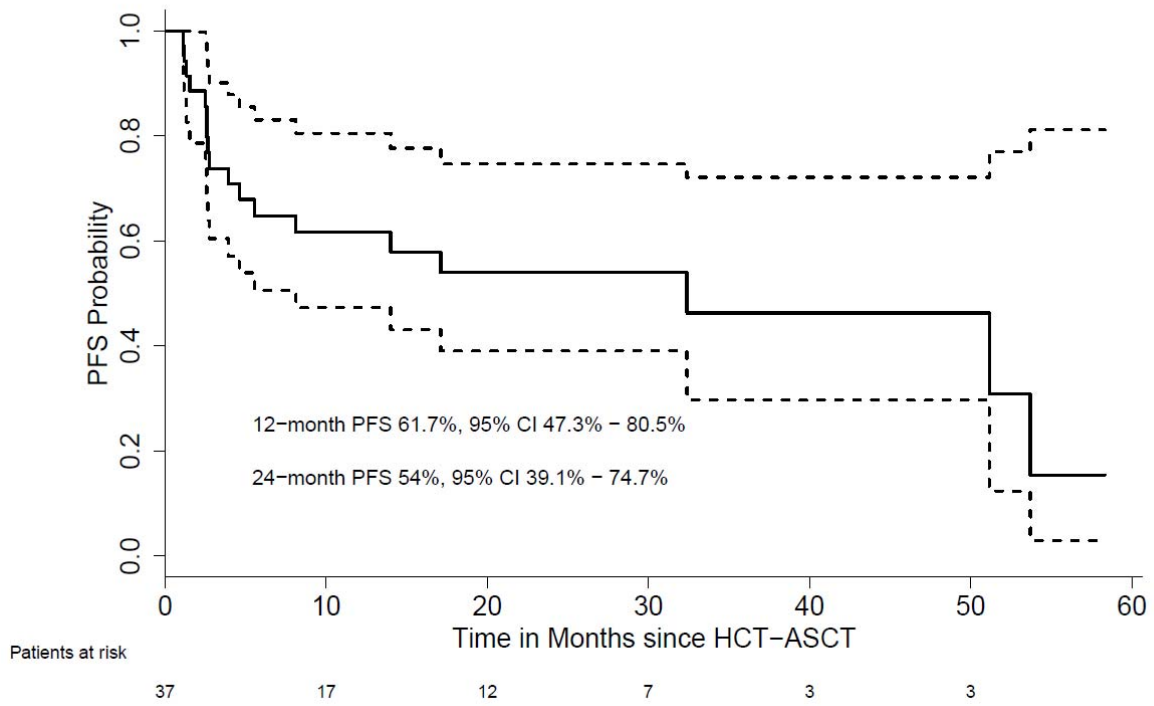
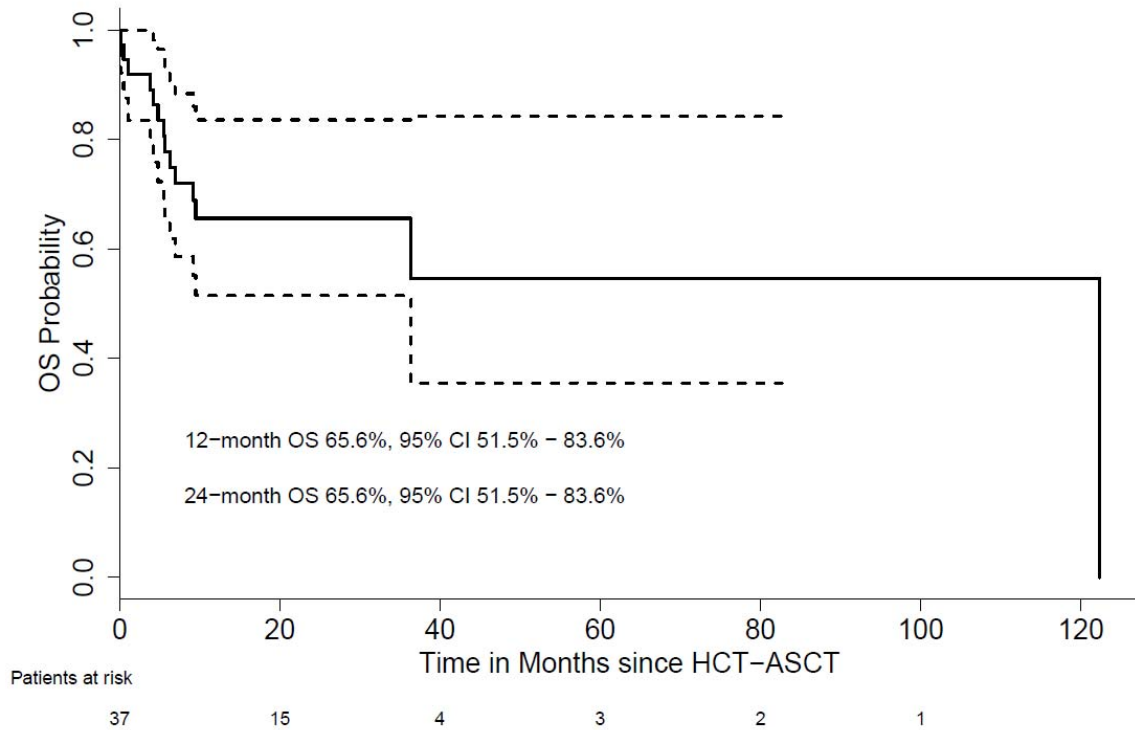


Figure 4

PFS in patients with HCT-ASCT at 2nd or later line

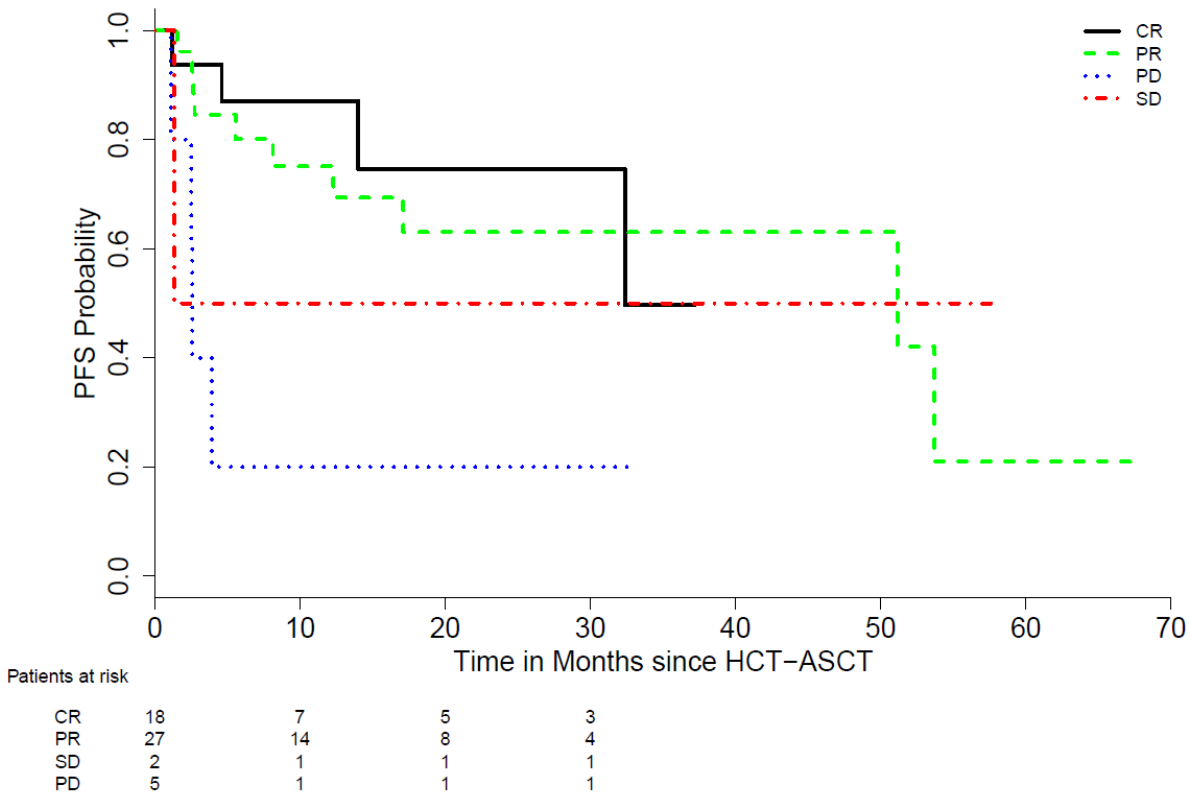


OS in patients with HCT-ASCT at 2nd or later line



Online Figure 1

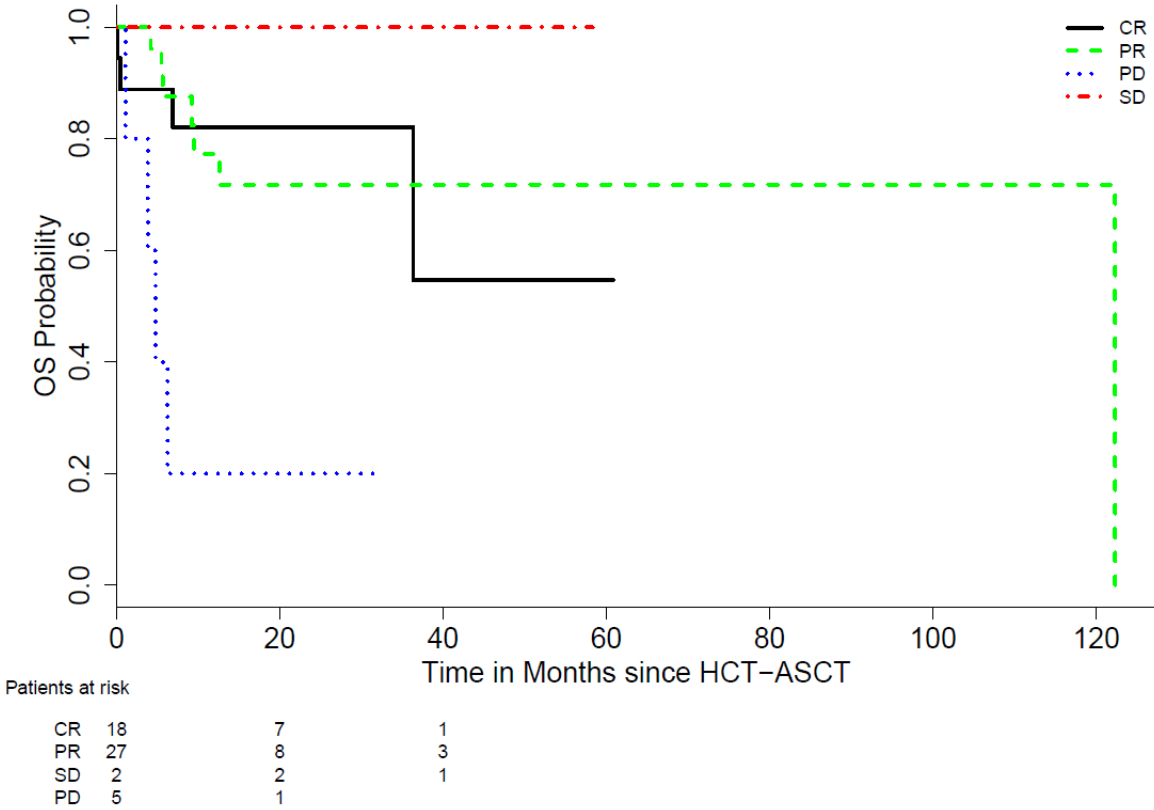
PFS stratified by remission before HCT-ASCT





Online Figure 2

OS stratified by remission before HCT-ASCT



## **Legend to Figures**

**Figure 1** Kaplan-Meier plot: Progression Free Survival from time of HDT-ASCT of all evaluable patients

**Figure 2** Kaplan-Meier plot: Overall Survival from time of HDT-ASCT of all patients

**Figure 3** Kaplan-Meier plot: Progression Free Survival and Overall Survival from time of HDT-ASCT for patients receiving HDT-ASCT during first-line therapy

**Figure 4** Kaplan-Meier plot: Progression Free Survival and Overall Survival from time of HDT-ASCT for patients receiving HDT-ASCT at second or later line of treatment

**Online Figure 1** Kaplan-Meier plot: Progression Free Survival from time of HDT-ASCT of all patients stratified by remission status before HDT-ASCT

**Online Figure 2** Kaplan-Meier plot: Overall Survival from time of HDT-ASCT of all patients stratified by remission status before HDT-ASCT