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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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Abstract

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

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

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

Introduction

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

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

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

Methods

Patient selection criteria and data collection

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

Statistical analysis

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

Results

Patient characteristics

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

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

Conditioning regimen and ASCT-specific data

The majority of patients was conditioned with TT 10-20 mg/kg + carmustine 320-400 mg/m^2 (61.5%). Remaining patients received TT 10-20 mg/kg + busulfan 3.2-6.4 mg/kg (13.5%), TT 250-750 mg/m² + busulfan 2.4–8.0 mg/kg + cyclophosphamide 60-120 mg/kg (13.5%) or TT 10 mg/kg as single agent (11.5%). Rituximab was additionally given in 2 patients (3.8%). The median number of reinfused CD34+ hematopoietic stem cells was 5.29 x 10^6/Kg (range 2.24 to 35). Median time to neutrophil engraftment was 10 days (range 6 to 34). We observed two

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

Treatment response and survival

Table 2 summarizes the response status after HDT-ASCT, stratified by line of therapy and remission status prior to HDT-ASCT. Following HDT-ASCT, 45 of 52 patients (86.5%) achieved an objective response (36 CR and 7 PR). One patient (1,9%) experienced SD whilst 5 (9.6%) had PD one month after HDT-ASCT.

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

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

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

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

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

Discussion

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

Strengths and limitations

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

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

Comparison to other studies

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

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

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

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

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

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

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

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

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

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

Conclusions

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

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Conflict of Interest

The authors declare no conflict of interest.

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Patient characteristics	**HDT applied in first line** N=15	**HDT applied in second/subsequent line** N=37	**Total** N=52
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

N° of patients	Trial design	median age (range)	HD-ASCT setting	Induction regimen	Conditioning regimen	WBRT	Follow-up (median)	OS	TRM	Reference
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, dexamathasone; BuCy, busulfan, cyclophosphamide; Cy, cyclophosphamide

Figure 1

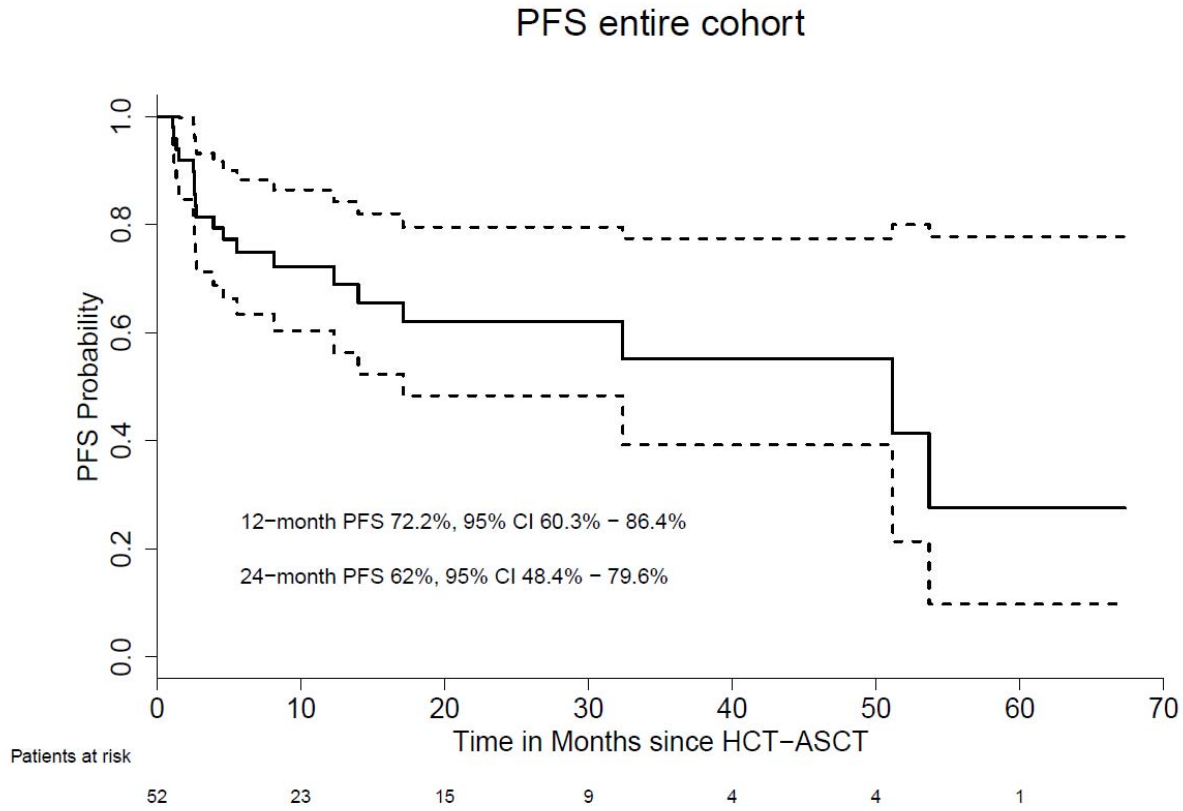

PFS entire cohort
PFS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month PFS 72.2%, 95% CI 60.3% − 86.4%
24−month PFS 62%, 95% CI 48.4% − 79.6%
0
10
20
30
40
50
60
70
Time in Months since HCT−ASCT
Patients at risk
52
23
15
9
4
4
1

Figure 2

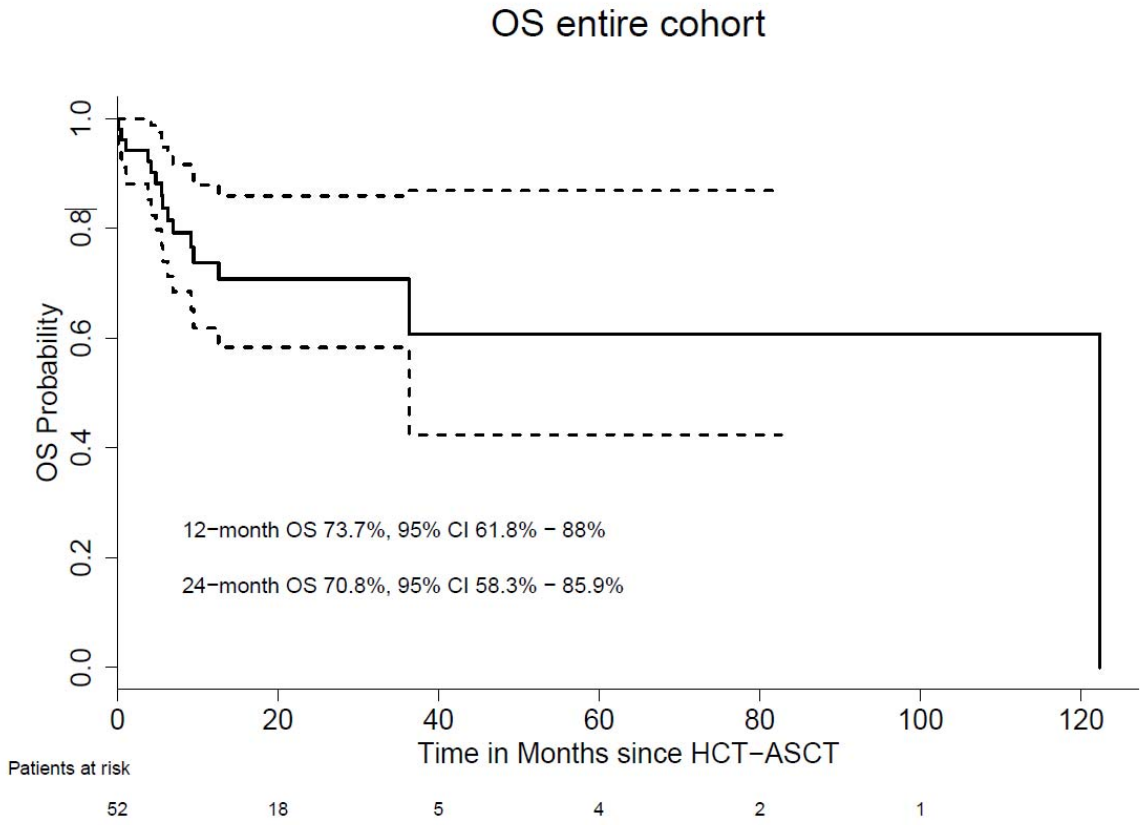
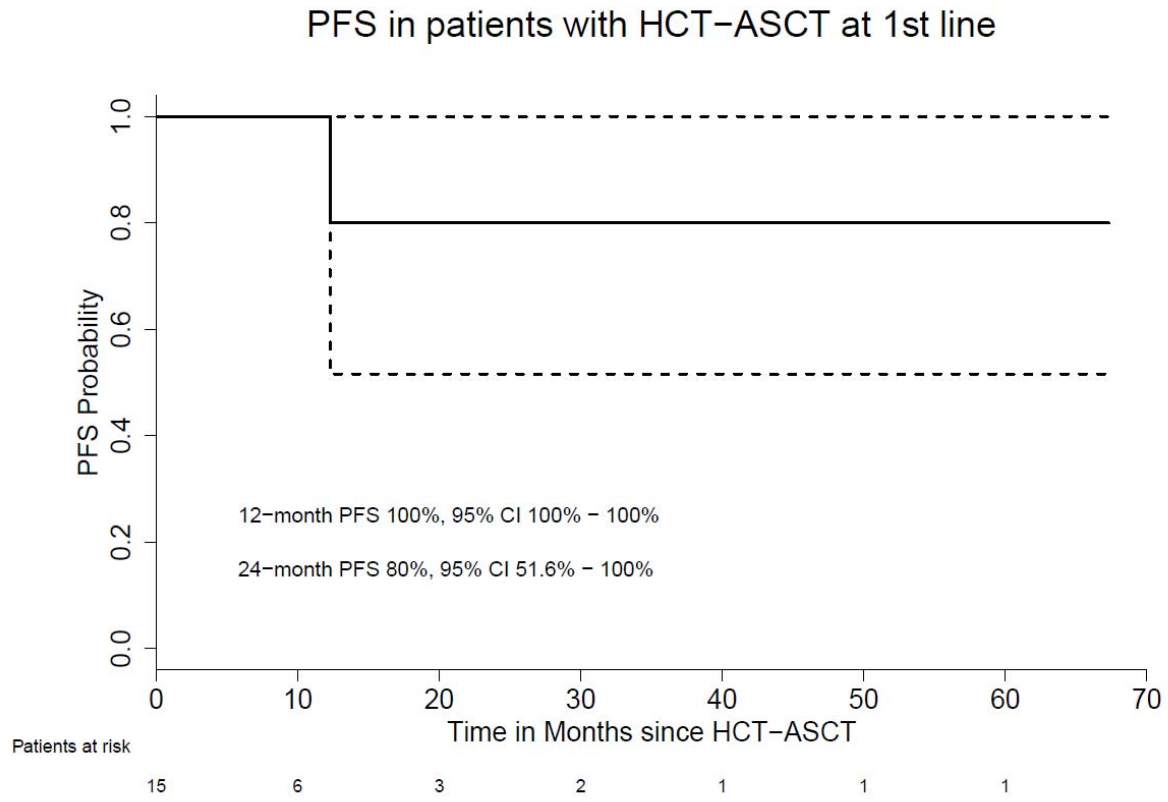

OS entire cohort
OS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month OS 73.7%, 95% CI 61.8% − 88%
24−month OS 70.8%, 95% CI 58.3% − 85.9%
0
20
40
60
80
100
120
Time in Months since HCT−ASCT
Patients at risk
52
18
5
4
2
1

Figure 3


PFS in patients with HCT−ASCT at 1st line
PFS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month PFS 100%, 95% CI 100% − 100%
24−month PFS 80%, 95% CI 51.6% − 100%
0
10
20
30
40
50
60
70
Time in Months since HCT−ASCT
Patients at risk
15
6
3
2
1
1
1

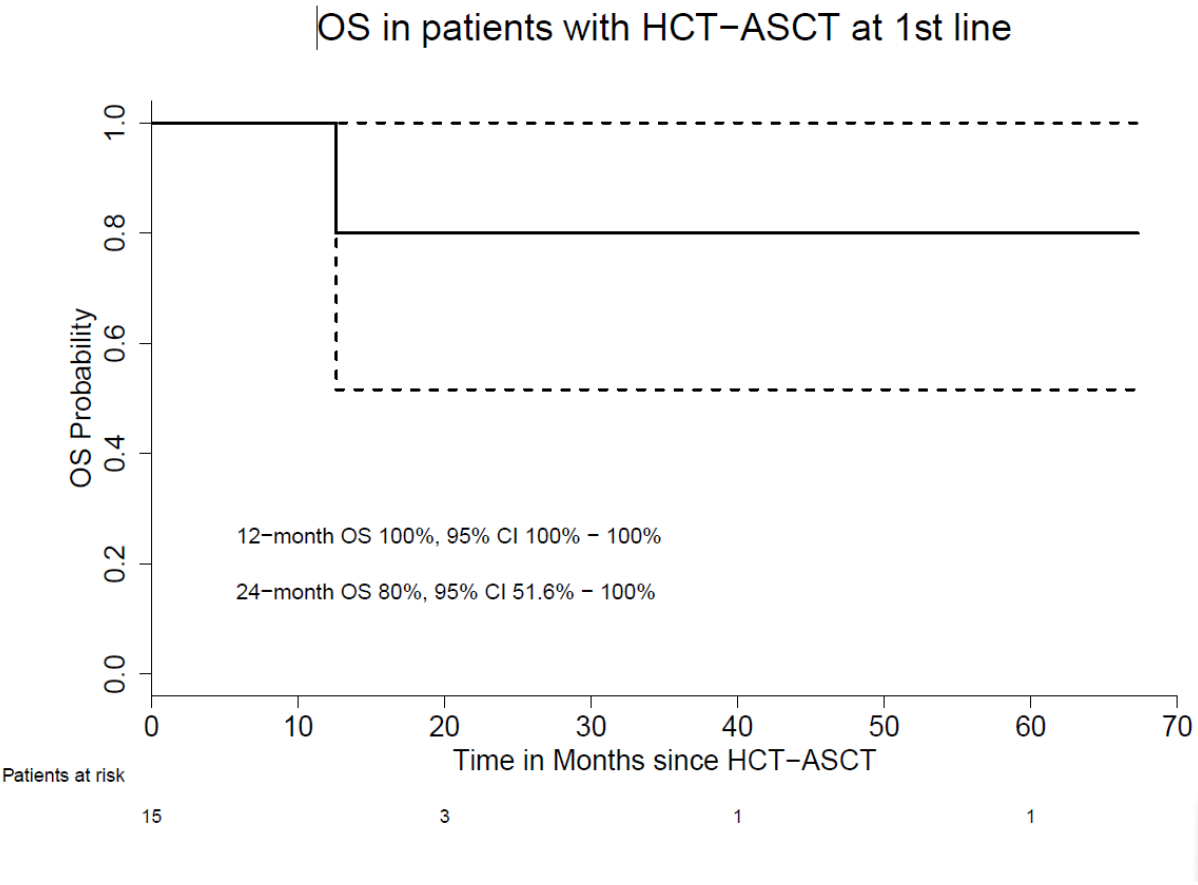
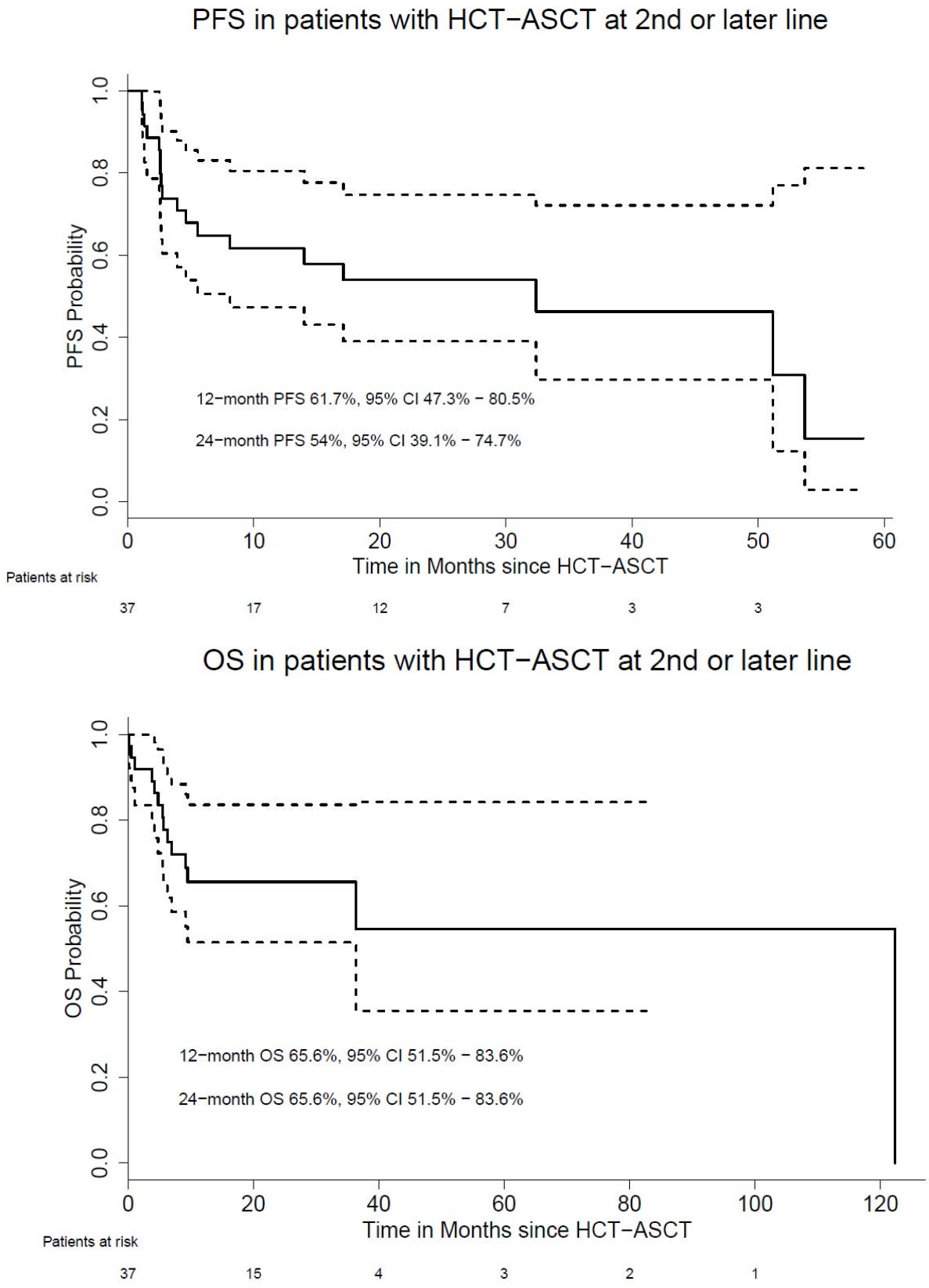
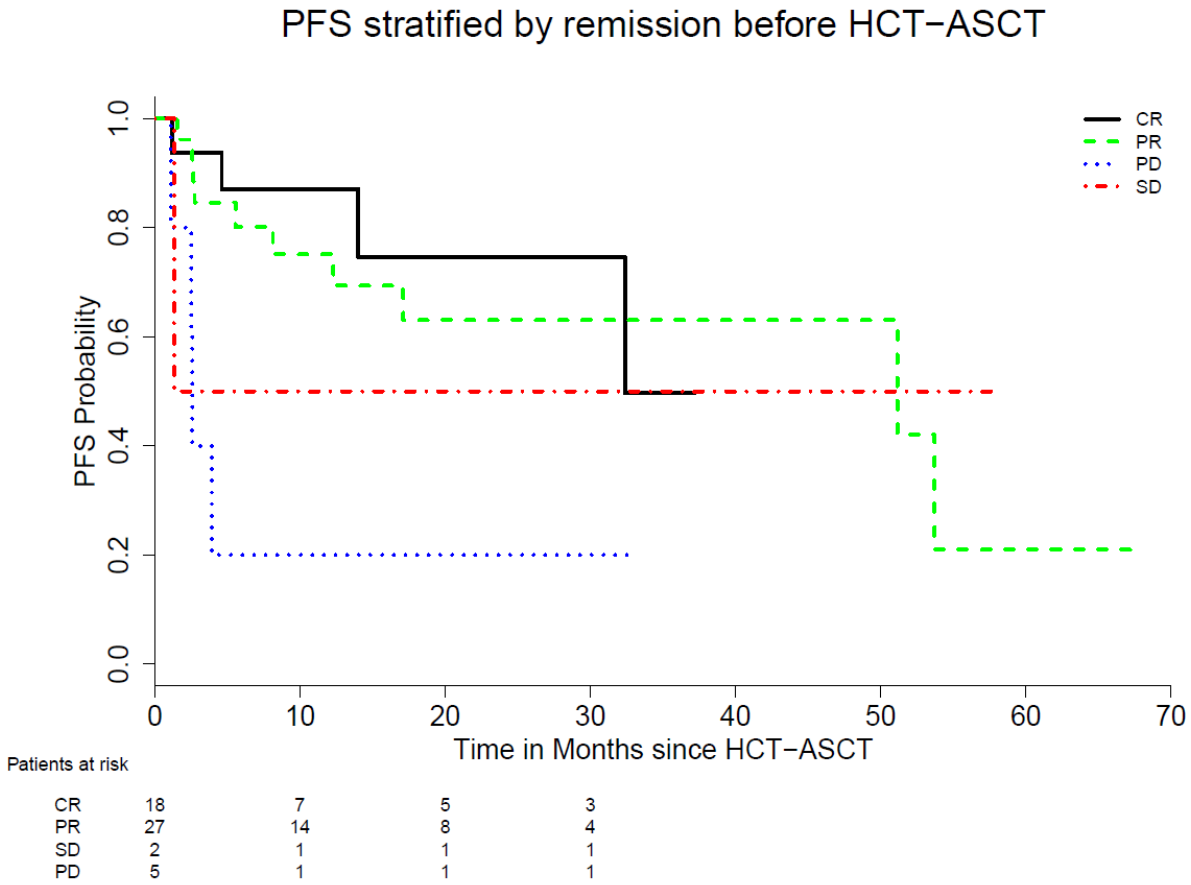

OS in patients with HCT−ASCT at 1st line
OS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month OS 100%, 95% CI 100% − 100%
24−month OS 80%, 95% CI 51.6% − 100%
0
10
20
30
40
50
60
70
Time in Months since HCT−ASCT
Patients at risk
15
3
1
1

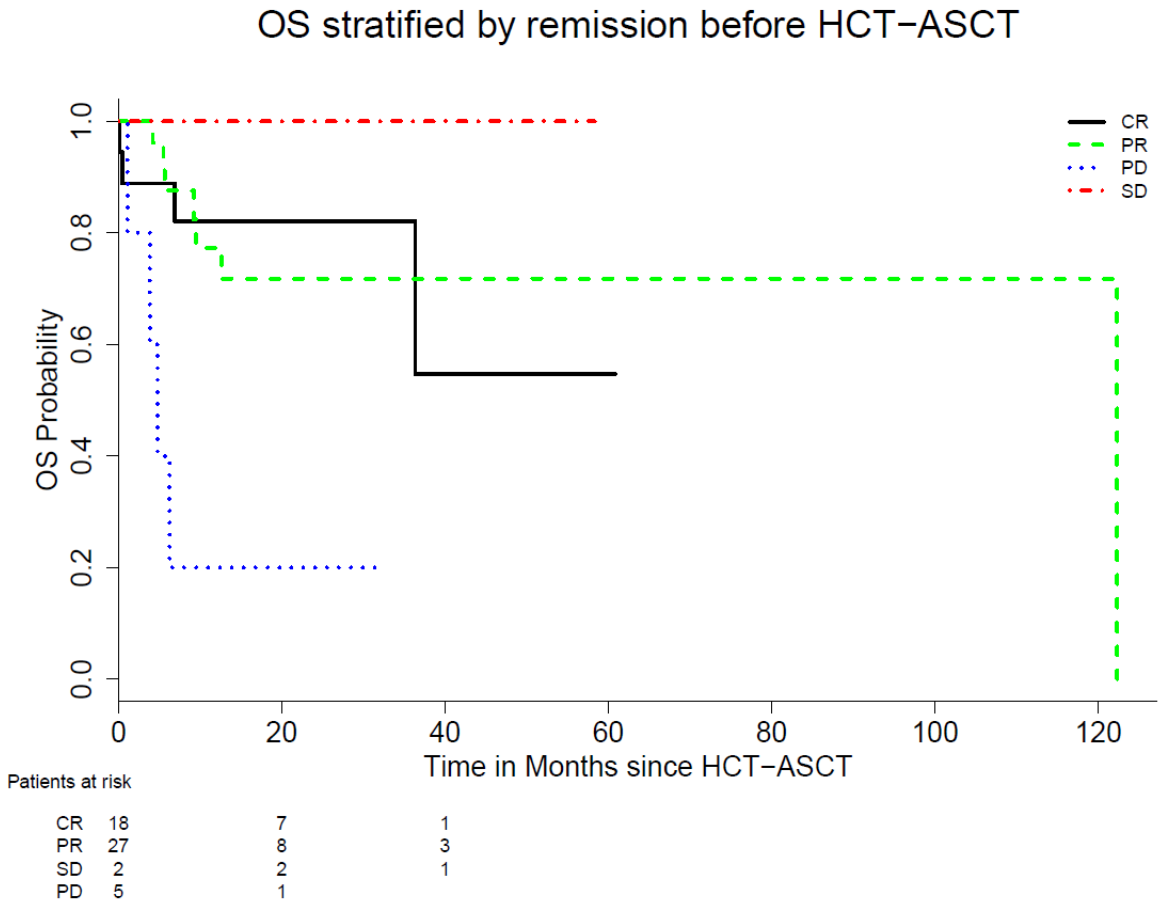
Figure 4


PFS in patients with HCT−ASCT at 2nd or later line
PFS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month PFS 61.7%, 95% CI 47.3% − 80.5%
24−month PFS 54%, 95% CI 39.1% − 74.7%
0
10
20
30
40
50
60
Time in Months since HCT−ASCT
Patients at risk
37
17
12
7
3
3
OS in patients with HCT−ASCT at 2nd or later line
OS Probability
0.0
0.2
0.4
0.6
0.8
1.0
12−month OS 65.6%, 95% CI 51.5% − 83.6%
24−month OS 65.6%, 95% CI 51.5% − 83.6%
0
20
40
60
80
100
120
Time in Months since HCT−ASCT
Patients at risk
37
15
4
3
2
1

Online Figure 1



Online Figure 2



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