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Impact of Pretransplantation ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography on Survival Outcomes after T Cell–Depleted Allogeneic Transplantation for Hodgkin Lymphoma

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Pretransplant ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography status is an important prognostic factor for outcomes after autologous stem cell transplantation (SCT) in Hodgkin lymphoma (HL), but its impact on outcomes after allogeneic SCT remains unclear. We retrospectively evaluated outcomes after T cell–depleted allogeneic SCT of 116 patients with nonprogressive HL according to pretransplant Deauville scores. Endpoints were overall survival (OS), progression-free survival (PFS), relapse rate (RR), and nonrelapse-related mortality (NRM). OS, PFS, and RR did not differ significantly between the Deauville 1 to 2 and Deauville 3 to 5 cohorts (OS: 77.5% versus 67.3%, $P = .49$; PFS: 59.4% versus 55.7%, $P = .43$; RR: 20.9% versus 22.6%, $P = .28$ at 4 years). Differences in PFS remained statistically nonsignificant when comparisons were made between Deauville 1 to 3 and Deauville 4 to 5 cohorts (60.9% versus 51.4%, $P = .10$), and RR remained very similar (21.5% versus 23.8%, $P = .42$). Multivariate analyses demonstrated trends toward significance for an effect of Deauville score on PFS (hazard ratio 1.82 for Deauville 4 to 5, $P = .06$) and for number of lines of prior therapy on OS (hazard ratio 2.34 for >5 lines, $P = .10$). The latter effect appeared to be driven by higher NRM rather than increased RR. Our findings suggest that Deauville score before allogeneic SCT in patients with nonprogressive HL has a relatively modest impact on survival outcomes in comparison with the impact in autologous SCT and that predictive values for the individual patient remain low, indicating that residual FDG-avid disease should not preclude allogeneic SCT. Furthermore, our findings bring into question the importance of attainment of metabolic complete response in this setting if it is at the expense of increasing NRM risk.

INTRODUCTION

Hodgkin lymphoma (HL) is a highly chemotherapy-responsive disease [1,2]. Approximately 20% to 30% of patients, however, will have primary resistant disease or will relapse after conventional chemotherapy. Standard management in these cases involves salvage chemotherapy, consolidated by autologous stem cell transplantation (ASCT) [3,4]. A number of factors inform prognosis after ASCT, including both clinical factors and response before ASCT [5]. In patients with chemotherapy-sensitive disease, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or combined-modality imaging incorporating PET with computed tomography (PET-CT) allows greater differentiation in this regard than can be achieved by CT alone [6-8]. PET is increasingly used to direct response-adjusted treatment

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algorithms for lymphoma, in many instances allowing risk stratification and either escalation or de-escalation of therapeutic intensity. Significant advances have been made in recent years with respect to quality assurance and standardization, with the introduction of a 5-point visual analysis score (Deauville score) [9]. Patients achieving a metabolic complete response (mCR) before ASCT have a predicted progression-free survival (PFS) rate of 70% to 80% at 3 to 5 years. In contrast, the equivalent PFS in those with residual FDG-avid disease is only 25% to 30%, even in the context of partially responsive disease as assessed by CT [7,10]. Brentuximab vedotin consolidation therapy improves PFS in patients who are at high risk of relapse after ASCT as assessed by clinical risk factors [11], and it is likely that much of this benefit is derived in those with residual metabolically active disease at the time of transplantation. Nevertheless, a significant proportion of these patients will subsequently relapse.

The application of PET to identify a high-risk cohort of patients predicted to have a relatively poor prognosis after ASCT allows exploration of other treatment strategies, such as allogeneic SCT (alloSCT) [12]. Historically, the benefit of alloSCT in lymphoma was limited by the toxicity of myeloablative procedures [13,14]. The development of reduced-intensity conditioning regimens improved nonrelapse-related mortality (NRM) rates, increasing long-term PFS rates in adult patients and further demonstrating the existence of a graft-versus-lymphoma effect [15-18]. Nevertheless, it remains unclear which patients will benefit most from this approach and when it should be considered in the overall treatment algorithm. In particular, the significance of residual metabolically active disease before transplant is less clear than in the ASCT setting, and data for specific subtypes of lymphoma such as HL are lacking. Resolving the answer to this question is clinically important for a number of reasons. First, it dictates to some degree how aggressively clinicians should attempt to achieve mCR before alloSCT, which impacts on likely levels of comorbidity and organ dysfunction present at the time of transplantation. Second, it will help to define how alloSCT might compare and integrate alongside other novel treatment strategies in this group of patients, for example, ASCT followed by brentuximab vedotin consolidation therapy or agents interfering with immunologic checkpoints [11,19]. Therefore, the present study evaluated the prognostic value of pretransplant PET-CT assessed according to Deauville criteria in a large multicenter cohort of patients with relapsed or refractory HL undergoing alloSCT using a T cell–depleted alemtuzumab-containing platform.

METHODS

Study Population

One hundred twenty-nine patients undergoing alloSCT for HL between August 2005 and August 2014, who had a PET-CT performed within 28 days pretransplant to which a Deauville score could be assigned, were identified at 4 UK transplant centers. Of these patients, 13 had progressive disease at the time of transplantation. Transplant outcomes in patients with progressive disease are known to be poor, and these patients were excluded from subsequent analyses, leaving a primary study cohort of 116 patients (Table 1). Post-transplant outcomes on 46 of these patients have previously been reported [12,17].

Study Design

The study was performed retrospectively. Digital file data from PET-CT scans were reviewed centrally to assign a Deauville score. To assess chemotherapy sensitivity, positive PET-CT scans were compared with images obtained either before the last line of salvage treatment or with those acquired at the time of relapse or first-line treatment failure. Importantly, all study sites were involved in prospective UK trials of PET-directed therapy in lymphoma, with attendant quality controls as part of the UK National Cancer Research Institute PET Research Network [20]. As such, centers complied with methods for quality control to ensure the performance of imaging equipment, data transfer, and image quality were within a prespecified acceptable range. Physicists from the core laboratory visited each PET center and scanned a standard plastic structure ("phantom") to check image quality and quantitative accuracy before starting these national studies. For the purposes of this study, progressive disease was defined as an increase greater than 30% in maximum standardized uptake value (SUV_{max}) at any single tumor lesion or development of a new FDG-avid disease-related lesion(s).

Table 1
Patient Characteristics According to Deauville Score

Characteristic	Overall (N = 116)	D1-2 (n = 49)	D3-5 (n = 67)	*P*
Median age at alloSCT, yr	30	30	29	.86*
Gender				
Female	51 (59)	57 (28)	46 (31)	
Male	49 (57)	43 (21)	54 (36)	.27†
Median number of prior treatment lines (range)‡	4 (2-10)	4 (3-10)	4 (2-10)	.68*
Prior ASCT				
No	74 (86)	69 (34)	78 (52)	
Yes	26 (30)	31 (15)	22 (15)	.39†
Donor source				
Sibling	41 (47)	30 (15)	48 (32)	
MUD	43 (50)	43 (21)	43 (29)	
MMUD	16 (19)	27 (13)	9 (6)	.08§
Conditioning				
BEAM-C	61 (71)	57 (28)	64 (43)	
FM-C	39 (45)	43 (21)	36 (24)	.45†
Year of transplant				
2005-2009	37 (43)	39 (19)	36 (24)	
2010-2014	63 (73)	61 (30)	64 (43)	.85†

MUD indicates matched unrelated donor; MMUD, mismatched unrelated donor.
Values are percent with number of patients in parentheses, unless otherwise noted.
* *P* derived using unpaired *t*-test.
† *P* derived using Fisher's exact test.
‡ Data not available for 6 patients.
§ *P* derived using Fisher's exact test comparing sibling donor to combined matched and mismatched unrelated donors.

Conditioning Regimen

All patients were transplanted using 1 of 2 previously described T cell–depleted regimens [21,22]: fludarabine, melphalan, and alemtuzumab (Campath) (FM-C) or carmustine, etoposide, cytarabine, melphalan, and alemtuzumab (Genzyme Corp, Cambridge, MA, USA) (BEAM-C). Thirteen patients from the BEAM-C regimen received lomustine (200 mg/m^2 on day −6) in place of carmustine because carmustine was not available. Patients who had failed a previous ASCT were more likely to receive the less intensive FM-C protocol (93% FM-C [28/30] versus 7% BEAM-C [2/30]). The stem cell source was a matched sibling donor in 47 cases, a matched unrelated donor in 50 cases, and a 1 to 2 antigen mismatched donor in 19 cases.

Post-Transplant Surveillance and Donor Lymphocytes

Restaging was performed post-transplant using PET-CT. Three study sites used a similar strategy with restaging at 3, 6, 9, 12, 18, and 24 months, using the definition outlined previously (see Study Design) for determining progressive disease. The fourth site (11 patients) followed a similar strategy in patients remaining mixed chimeras, although routine scanning in patients achieving full-donor chimerism was discontinued and further imaging was performed only if clinical suspicion of relapse in such cases. In the absence of contraindications, donor lymphocyte infusions were routinely administered for the treatment of mixed chimerism (considered as "prophylactic") or relapse (considered as "therapeutic") as previously described [17].

Study Endpoints and Statistical Analysis

The primary outcome measures were overall survival (OS), PFS, NRM, and relapse rate (RR). Statistical analyses were performed using NCSS 10 software (NCSS, Kaysville, UT, USA). Survival curves were estimated by Kaplan-Meier analyses and comparisons performed by the log-rank method.

OS was defined as the time from transplant to death from any cause. PFS was defined as the time from transplant to the time of progression, relapse, or death from any cause. NRM and RR were calculated by cumulative incidence analyses. NRM was the time to death with relapse as the competing risk, and RR was the time to relapse or progression, with death without relapse the competing risk. Comparisons of cumulative incidence analyses were performed using Gray's test. The Cox proportional hazards model was used to for multivariate analyses.

RESULTS

Patient Characteristics

Patient characteristics are presented in Table 1. The median age at transplantation was 30 years (range, 12 to 66), and the median number of prior lines of treatment was 4 (range, 2 to 10). Front-line therapy was adriamycin, bleomycin, vinblastine, and dacarbazine in most patients, although a small number received pediatric regimens or bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisolone. First-line salvage consisted of a platinum-based regimen in most patients (most commonly etoposide, methylprednisolone, cytarabine, and cisplatin). Median follow-up in surviving patients was 2.8 years. The Deauville score was 1 to 2 (PET-CT negative, mCR) in 49 patients, 3 in 13, and 4 in 36 and 5 in 18 (Table 1). Using this definition, 42% (49/116) underwent transplant in mCR, whereas the remaining 58% (67/116) had residual disease. There were no significant differences in terms of median age at transplant, gender, number of lines of prior therapy, prior ASCT, donor source, conditioning regimen, or year of transplant between the Deauville 1 to 2 (D1-2) and Deauville 3 to 5 (D3-5) cohorts (Table 1). Notably, there were also no differences between these cohorts in terms of the numbers subsequently receiving donor lymphocyte infusions for mixed chimerism (D1-2, 11/49 [22.4%]; D3, 3/13 [23.1%]; and D4-5, 14/54 [25.9%]), and the analyses of RR and PFS are therefore not confounded by any related bias. Sixteen patients received donor lymphocyte infusions after relapse (D1-2, 9/49 [18.4%]; D3, 2/13 [15.4%]; and D4-5, 5/54 [9.3%]).

Impact of PET-CT Status before AlloSCT on OS and PFS

At the time of analysis, 84 patients were alive and 32 had died. Rates of acute and chronic graft-versus-host disease were relatively low and in keeping with prior reports using alemtuzumab-based conditioning (grade II acute graft-versus-host disease in 25%, grade III to IV acute graft-versus-host disease in 5%, and chronic graft-versus-host disease in 23%, most of which was limited). There was no statistically significant difference in OS between the D1-2 and D3-5 cohorts (77.5% [95% confidence interval [CI], 65.1% to 90.0%] versus 67.3% [95% CI, 54.7% to 79.8%], respectively, at 4 years, $P = .49$) (Figure 1A). Furthermore, there was no statistically significant difference in PFS (59.4% [95% CI, 43.6% to 75.3%] versus 55.7% [95% CI, 42.7% to 68.8%] at 4 years, $P = .28$) (Figure 1B). Deaths in the PET-CT "positive" group tended to occur earlier than in the PET-CT "negative" group, with early divergence of survival curves followed by later convergence after year 4. It should be noted that all late events in the OS of the D1-2 cohort were due to disease-related deaths occurring at later time points (Figure 1A).

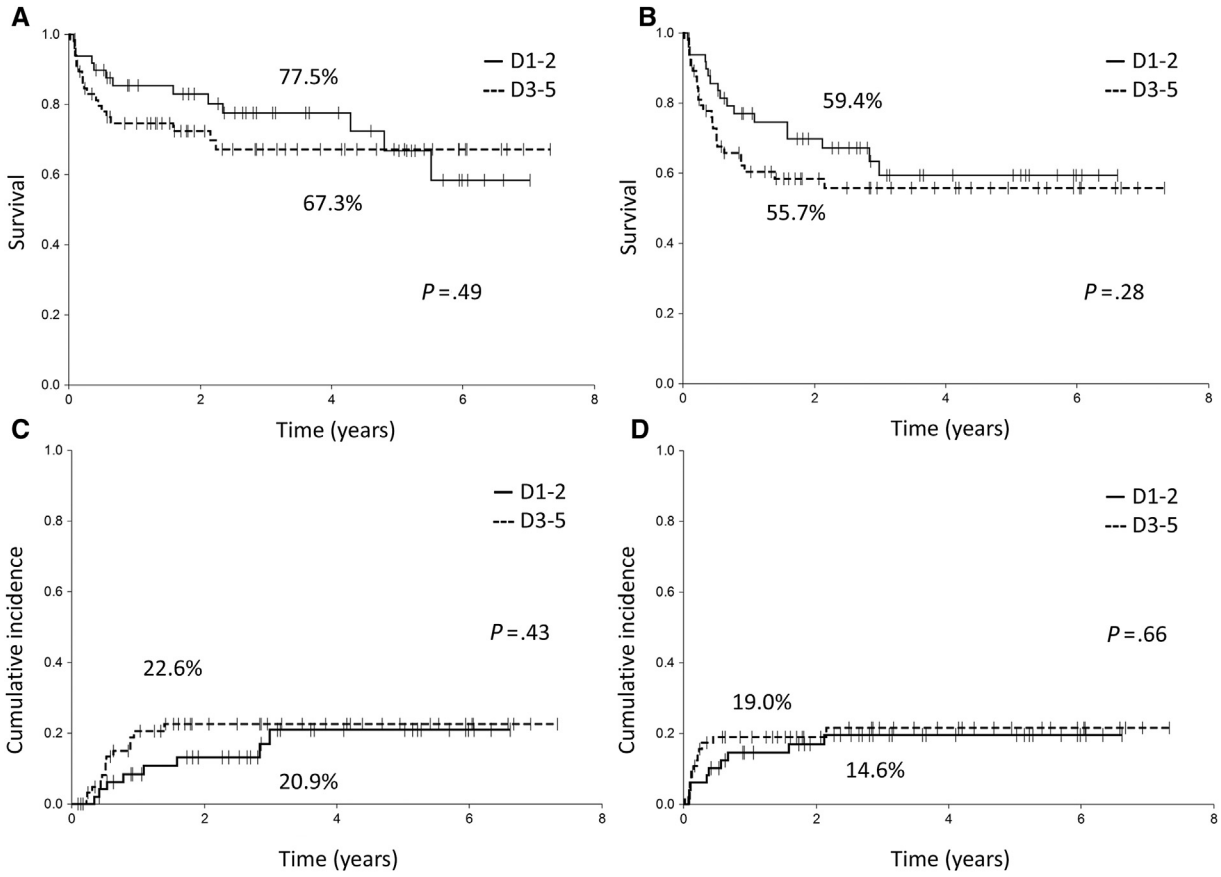

Figure 1. Survival outcomes according to pretransplant Deauville score: D1-2 versus D3-5. Percentages on graph show 4-year rates for each outcome, except NRM at 1 year. *P* values are shown for each comparison. (A) OS, (B) PFS, (C) RR, and (D) NRM, comparing D1-2 versus D3-5.

Impact of PET-CT Status before AlloSCT on RR and NRM

The RR was not significantly different between the D1-2 and D3-5 cohorts (4-year RR 20.9% [95% CI, 11.0% to 22.9%] and 22.6% [95% CI, 14.0% to 36.5%], respectively, $P = .43$). Relapse, however, tended to occur earlier in patients with residual metabolically active lesions pretransplant, reflecting the earlier deaths seen on the OS curves (Figure 1C). Similarly, there was no difference in NRM at 1 year (14.6% [95% CI, 7.3% to 28.9%] versus 19.0% [95% CI, 11.4% to 31.7%], $P = .66$) or beyond (Figure 1D).

Comparison of Outcomes for Deauville Score 1 to 3 versus Deauville Score 4 to 5

A negative PET scan is by convention defined by a Deauville score of 1 or 2. However, in some clinical scenarios a Deauville score of 3 may also be considered to represent a mCR [23], particularly in cases where response-adjusted modification of therapy is directed toward an escalation strategy. Survival outcomes were reanalyzed comparing D1-3 versus D4-5. There was no significant excess mortality for the D4-5 group, although trends toward worse survival outcomes were more evident (4-year OS 79.7% [95% CI, 68.6% to 90.7] versus 62.2% [95% CI, 48.1% to 76.3], $P = .14$; 4-year PFS 60.9% [95% CI, 46.2% to 75.5%] versus 51.4% [95% CI, 36.9% to 66.0%], $P = .10$, for D1-3 versus D4-5, respectively) (Figure 2A,B). RRs remained remarkably similar between the 2 cohorts (4-year RR 21.5% [95% CI, 11.8% to 39.0%] versus 23.8% [95% CI, 14.2% to 39.9%], respectively, $P = .42$) (Figure 2C), with modest but nonsignificant differences in NRM (1-year NRM 13.2% [95% CI, 6.9% to 25.2%] versus 21.9% [95% CI, 13.0% to 37.0%], $P = .28$) (Figure 2D).

Effect of Disease Burden on Outcome in Those with Residual FDG-Avid Lesions

To further investigate whether survival was affected by the bulk/extent of residual disease, exploratory analyses were performed comparing the outcomes of patients with Deauville score 4 with those of patients with Deauville score 5. Recognizing that the numbers in each cohort were small, there were no evidence that survival outcomes were inferior in those with a Deauville score of 5 (4-year OS 61.9% [95% CI, 44.6% to 79.1%] versus 62.2% [95% CI, 37.6% to 86.9%], $P = .74$; PFS 45.6% [95% CI, 27.9% to 63.3%] versus 61.8% [95% CI, 36.9% to 86.7%], $P = .24$; RR 26.9% [95% CI, 14.9% to 48.6%] versus 17.7% [95% CI, 6.3% to 49.3%], $P = .55$, for D4 and D5, respectively; data not shown).

Univariate Analysis of Other Factors Influencing Outcomes

A number of characteristics other than pretransplant PET-CT status were also assessed for impact on transplant outcomes by univariate analyses (Table 2). Neither age (data not shown), year of transplant (2005 to 2009 versus 2010 to

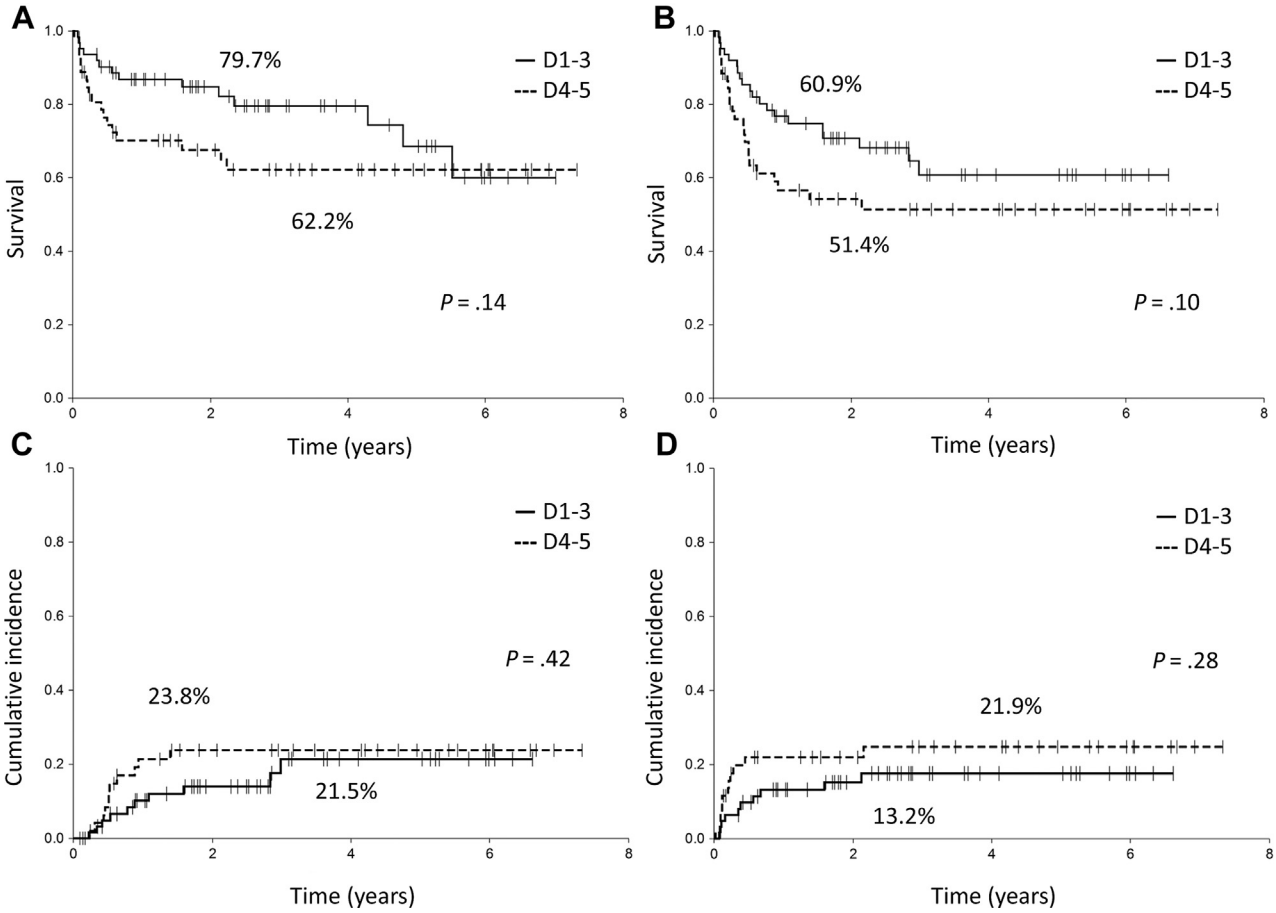

Figure 2. Survival outcomes according to pretransplant Deauville score: D1-3 versus D4-5. Percentages on graph show 4-year rates for each outcome, except NRM at 1 year. *P* values are shown for each comparison. (A) OS, (B) PFS, (C) RR, and (D) NRM, comparing D1-3 versus D4-5.

Table 2
Univariate Analysis of Survival Outcomes

Variable factor	4-Year OS [95% CI]	4-Year PFS [95% CI]	4-Year RR [95% CI]	1-Year NRM [95% CI]
Donor source				
Sibling	73.3 [59.2-87.3]	53.6 [37.6-69.5]	25.4 [14.8-43.9]	14.9 [7.5-29.5]
Unrelated	72.0 [60.5-83.4]	61.3 [48.5-74.1]	19.4 [11.2-33.7]	19.3 [11.6-32.1]
P	.6990	.7974	.7068	.9676
Conditioning				
BEAM-C	76.8 [65.8-87.9]	67.9 [56.0-79.8]	16.1 [9.1-28.4]	13.4 [7.3-24.7]
FM-C	64.9 [50.4-79.4]	44.4 [28.6-60.2]	28.1 [16.8-47.1]	22.4 [12.9-38.6]
P	.1682	.0652	.3507	.1745
No. prior lines				
2-3 (n = 45)	80.6 [68.3-92.8]	62.8 [47.4-78.2]	20.6 [10.9-38.7]	13.6 [6.5-28.7]
4-5 (n = 41)	67.8 [51.4-84.1]	59.1 [42.0-76.2]	23.0 [12.5-42.5]	13.3 [5.9-30.1]
6-10 (n = 24)	56.0 [35.3-76.7]	44.8 [22.6-67.0]	16.2 [5.5-47.6]	34.2 [19.5-60.1]
P	.0773	.3005	.8284	.1657
Prior ASCT				
No	74.4 [64.1-84.7]	63.4 [52.4-74.5]	19.9 [12.6-31.4]	14.6 [8.7-24.7]
Yes	64.6 [46.8-82.3]	43.4 [23.2-63.6]	25.3 [12.4-51.9]	24.1 [12.6-45.9]
P	.2125	.2288	.9877	.1431
Year of transplant				
2005-2009	72.9 [59.2-86.6]	57.0 [41.5-72.5]	25.3 [14.8-43.3]	12.5 [5.5-28.4]
2010-2014	71.8 [60.0-83.5]	56.7 [41.8-71.5]	21.1 [11.4-38.9]	19.6 [12.2-31.4]
P	.7668	.9212	.4613	.4665

Values are percents.

2014), nor donor source (sibling versus unrelated) significantly influenced survival or RR.

Patients receiving conditioning based on BEAM-C demonstrated a clear trend toward superior PFS compared with those receiving FM-C. Both RR and NRM were higher in the FM-C group, although neither reached statistical significance. It is notable, however, that the cohorts receiving BEAM-C and FM-C were, to a large degree, clinically distinct. The more intensive BEAM-C regimen was generally used for patients earlier in the treatment pathway, rarely after failure of prior ASCT, and more commonly in those with fewer lines of prior therapy.

The number of lines of treatment before alloSCT had a greater influence on survival, with a trend toward better OS in the less heavily pretreated patients (Table 2, Figure 3A). This appeared to relate to excess NRM in the more heavily pretreated group ($P = .17$) (Figure 3D). There was no evident impact on PFS or RR with respect to number of lines of therapy (Figure 3B and 3C). Prior ASCT did not adversely affect outcomes per se (Table 2).

Multivariate Analysis of Factors Influencing Outcomes

Cox regression analyses were performed to evaluate independent impact of Deauville score, conditioning regimen, and number of lines of prior therapy. Analyses were performed using D1-2 versus D3-5 (Table 3) and D1-3 versus D4-5 (Table 4). Because no variables impacted on RR in univariate analyses, multivariate analyses were not performed for this outcome. Conditioning regimen was not significant in the multivariate analyses, consistent with the suggestion that the trends noted in the univariate analyses related to differences in the patient populations receiving the alternative regimens rather than an impact of the regimen itself. The strongest trends for independent significance in the OS analyses related to the number of prior treatment lines (hazard ratio 2.34 to 2.49 for >5 lines of treatment, $P = .08$ to .10; Tables 3 and 4). This was mirrored in the NRM analyses (hazard ratio 2.29 to 2.42 for >5 lines of treatment, $P = .14$ to .15; Tables 3 and 4). In the PFS analyses there was a trend toward an adverse impact of higher Deauville score when the D4-5 cohort was compared with the D1-3 cohort (hazard ratio 1.82, $P = .06$) (Table 4).

DISCUSSION

These data are important for a number of reasons, being derived from a relatively large and homogeneously treated series of patients from 4 UK transplant centers. Although we were unable to demonstrate statistically significant worse clinical outcomes in those with residual FDG-avid lesions before T cell–depleted alloSCT in this nonprogressive HL cohort, there was a trend for inferior PFS in those with Deauville scores of 4 to 5. The results are consistent with relatively modest differences in PFS, and a larger dataset is required to provide sufficient power to definitively detect such differences. Nevertheless, if such differences occur, they are relatively small, suggesting that this high-risk group of patients should not be excluded from consideration of alloSCT, because the positive or negative predictive value of the pretransplant scan is low for the individual patient. This is an important consideration, because it indicates that alloSCT can overcome some of the negative impact that is apparent in the ASCT setting.

The lack of impact of Deauville score on RR is surprising, although the findings extend upon and support our previous smaller prospective study, which included only 20 patients with HL [24]. The relapse kinetic did appear to differ according to Deauville score, tending to occur earlier in those with residual FDG-avid disease, resulting in an early divergence and later convergence of the RR curves. This might partially explain the discrepancy between the present study and a previous analysis including 46 patients with HL [25] that found an adverse outcome in terms of RR for patients with a positive PET-CT scan. Although the PET-CT positive HL cohort had a higher RR and worse OS and PFS than the PET-CT negative group in this prior study, survival outcomes were only demonstrated to 36 months after transplantation. Furthermore, the Deauville scoring system was not used. It is also possible that differences in transplantation platforms are important. Transplant conditioning was particularly heterogeneous in the prior study, and T cell depletion was not used in most patients. Finally, it is notable that the survival outcomes in the PET-CT positive group in the prior study were particularly poor (3-year OS and PFS rates of 28% and 30%, respectively) compared with the present study (4-year OS and PFS rates of 67% and 56%, respectively).

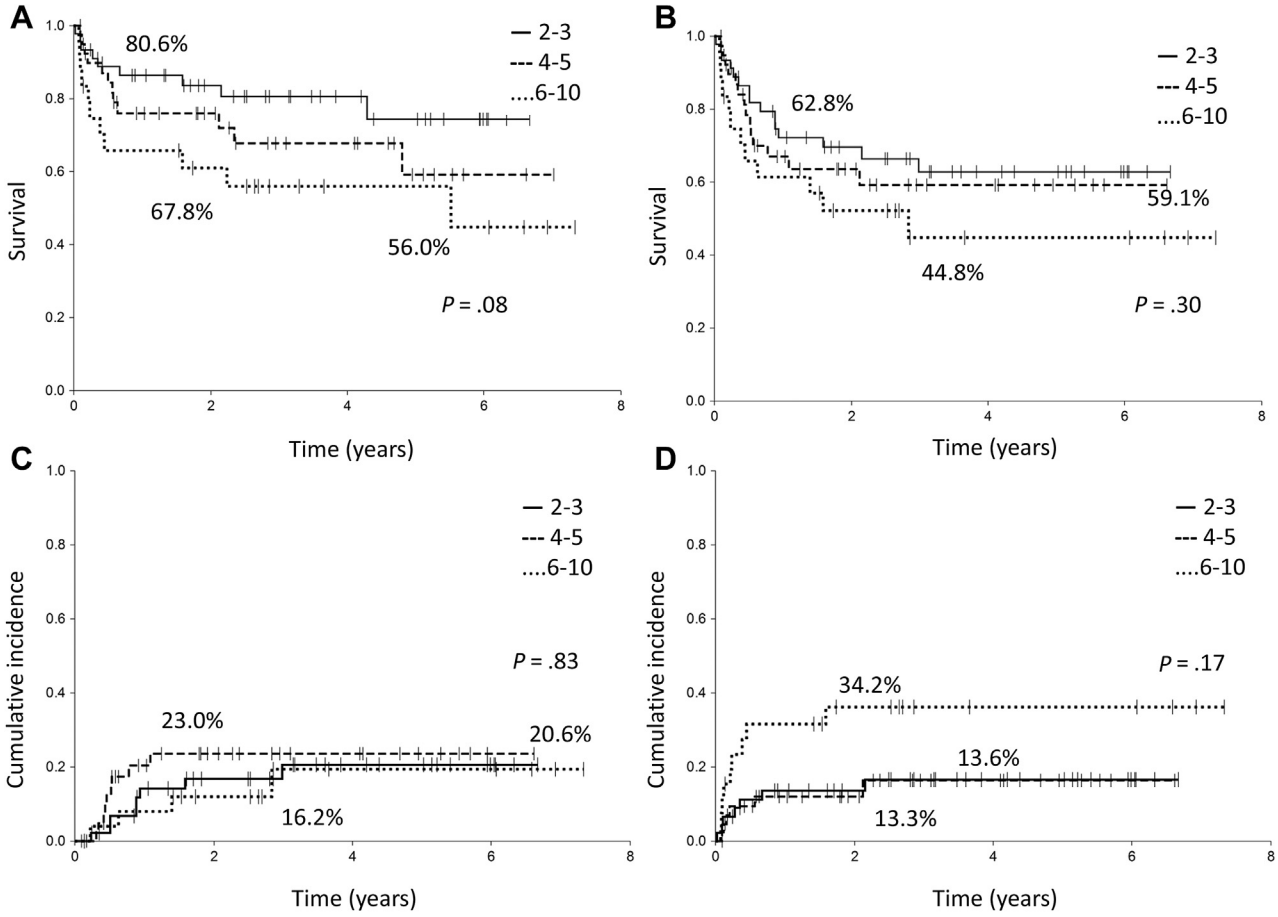

Figure 3. Effect of number of prior lines of treatment on outcome. Percentages on graph show 4-year rates for each outcome, except NRM at 1 year. Patients grouped according to number of prior lines as indicated in key. *P* values are shown for the comparison between all three curves. (A) OS, (B) PFS, (C) RR, and (D) NRM.

The finding that survival outcomes are worse in more heavily pretreated patients is less surprising, although the apparent correlation with higher NRM rather than higher RR is interesting. This brings into question the need to strive for mCR before alloSCT. From a clinical perspective, it seems likely that the additional salvage just helps to identify a group that would do marginally better with the transplant rather than improving transplant outcomes per se. If those failing to achieve mCR are still considered candidates for alloSCT, then further salvage may ultimately be counterproductive if it results in comorbidities that ultimately impact on alloSCT outcomes by increasing NRM. This differentiates possible decision algorithms in the ASCT setting, where persistent FDG avidity may act as a trigger to consider alternative therapies because of the greater difference between outcomes in PET positive and negative cases.

The main limitation of this study is that it is retrospective. Nevertheless, all centers used PET-CT facilities participating in national lymphoma trials and subject to rigorous quality control, and PET-CT data were subject to central review. The time period over which patients were transplanted is also relatively long. It is notable, however, that there have been no significant changes in transplant practice over this period, including supportive care therapies, and that there were no differences in terms of pretransplant Deauville score

Table 3
Multivariate Analysis of OS, PFS, and NRM comparing Deauville 1-2 vs 3-5

	OS		PFS		NRM	
	HR	*P*	HR	*P*	HR	*P*
Deauville score						
1-2	1.00	—	1.00	—	1.00	—
3-5	1.40	.3593	1.52	.1947	1.39	.4586
Conditioning						
BEAM-C	1.00	—	1.00	—	1.00	—
FM-C	1.27	.6236	1.63	.1840	1.35	.5500
Prior lines						
2-3	1.00	—	1.00	—	1.00	—
4-5	1.61	.3002	1.09	.8362	1.00	.9974
6-10	2.49	.0805	1.41	.4498	2.42	.1375

HR indicates hazard ratio.

Table 4
Multivariate Analysis of OS, PFS, and NRM comparing Deauville 1-3 vs 4-5

	OS		PFS		NRM	
	HR	*P*	HR	*P*	HR	*P*
Deauville score						
1-3	1.00	—	1.00	—	1.00	—
4-5	1.65	.1606	1.82	.0571	1.59	.2757
Conditioning						
BEAM-C	1.00	—	1.00	—	1.00	—
FM-C	1.24	.5967	1.60	.1916	1.34	.5517
Prior lines						
2-3	1.00	—	1.00	—	1.00	—
4-5	1.59	.3067	1.08	.8391	.99	.9814
6-10	2.34	.0971	1.34	.5170	2.29	.1555

according to year of transplant (Table 1) and no impact of year of transplant on transplant outcomes (Table 2). We believe therefore that this work further confirms the validity of the T cell–deplete reduced-intensity conditioning alloSCT approach for relapsed and refractory HL. It is also important to note that survival outcomes reported here are particularly favorable compared with those reported in the literature, which may reflect a unique effect of this alemtuzumab-based transplant strategy. As such, it remains unclear whether the results would be mirrored in T cell–replete transplant cohorts. The results reinforce the encouraging OS and PFS rates noted in earlier studies using alemtuzumab-based conditioning [26,27]. In those with 5 or fewer prior lines of treatment, the NRM rate was <15% and PFS rate >60%. Notably also, RR was <25% in this extended cohort. Furthermore, it is also notable that neither age nor donor source was an independent variable for survival, indicating that this strategy is potentially widely applicable. Indications for allogeneic transplantation in HL remain contentious. The strategy detailed in this article is in line with current UK guidelines, which have themselves been informed by the data shown here [28].

In conclusion, these data illustrate that the allogeneic graft-versus-HL effect can largely overcome the adverse prognostic impact of residual metabolically active disease that has been demonstrated before ASCT. Although relapse tended to occur earlier in those with residual FDG-avid disease at the time of alloSCT, further follow-up demonstrated that these patients were not significantly disadvantaged with regards OS and PFS at later time points. Such patients should, therefore, be considered for alloSCT, with consideration given to limiting the number of salvage regimens administered in those demonstrating chemotherapy sensitivity. Further work is justified to establish optimal parameters for the application of a response-adapted strategy for the use of reduced-intensity conditioning alloSCT in relapsed and refractory HL.

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