High-risk stage IIB Hodgkin lymphoma treated in the H10 and AHL2011 trials: total metabolic tumor volume is a useful risk factor to stratify patients at baseline

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Abstract

Stage IIB Hodgkin lymphoma (HL) patients, with a mediastinum-to-thorax (M/T) ratio of ≥0.33 or extranodal localization have a poor prognosis and are treated either as limited or advanced stage. We compared these two approaches in patients included in two randomized phase III trials enrolling previously untreated early (H10) or advanced stage HL (AHL2011). We included HL patients with Ann-Arbor stage IIB with M/T ≥0.33 or extranodal involvement enrolled in the H10 or AHL2011 trials with available positron emission tomography at baseline (PET0) and after two cycles of chemotherapy (PET2). Baseline total metabolic tumor volume (TMTV) was calculated using the 41% SUV_{max} method. PET2 response assessment used the Deauville score. One hundred and fourty-eight patients were eligible, including 83 enrolled in the AHL2011 trial and 65 in the H10 trial. The median TMTV value was 155.5 mL (range, 8.3-782.9 mL), 165.6 mL in AHL2011 and 147 mL in H10. PET2 positivity rates were 16.9% (n=14) and 9.2% (n=6) in AHL2011 and H10 patients, respectively. With a median follow-up of 4.1 years (95% confidence interval [CI]: 3.9-4.4), overall 4-year PFS was 88.0%, 87.0% in AHL2011 and 89.2% in H10. In univariate and mutivariate analyses, baseline TMTV and PET2 response influenced significantly progression-free survival (hazard ratio [HR]=4.94, HR=3.49 respectively). Notably, among the 16 patients who relapsed, 13 (81%) had a baseline TMTV baseline ≥155 mL. Upfront ABVD plus radiation therapy or upfront escBEACOPP without radiotherapy provide similar patient's outcome in high-risk stage IIB HL. TMTV is useful to stratify these patients at baseline.

Introduction

Recent clinical trials report the long-term survival rates in classical Hodgkin lymphoma (HL) depend on age and disease stage, but are as high as 90-95% at 10 years.[1] Accurate pretreatment stratification based on clinico-biological scores and baseline fluorodeoxyglucose (FDG) positron emission tomography (PET) and interim PET results for chemosensitivity to treatment are the main tools for selecting risk-adapted therapies in HL patients. Before the PET era, significant efforts were invested in the validation of clinically and internationally accepted scoring, which are still used in routine practice. Ann Arbor stage, number of involved lymph node areas, bulky mediastinal mass, extranodal involvement, erythrocyte sedimentation rate, and B-symptoms were the major factors for patientsstratification in the European Organization for Research and Treatment of Cancer/Lymphoma Study Association (EORTC/LYSA) or the German Hodgkin Study Group (GHSG) systems.[2] Standard care in patients with early disease includes two to four cycles of chemotherapy followed by radiation therapy (combined modalities)[3,4] and in patients with advanced-stage disease it is six cycles of chemotherapy.[5] Stage IIB with bulky or extranodal disease ('high-risk' IIB) were considered as advanced disease in the GHSG scoring system and treated accordingly with six cycles of escalated BEACOPP (escBEACOPP) chemotherapy, while they were considered as unfavorable early stage in the EORTC/LYSA scoring system and treated with combined modalities using an upfront ABVD chemotherapy regimen.

Thus, there is no properly established standard of care in this subset of patients. The high-risk IIB patient population represent 10-15% of early stage patients[4,6,7] in some series, but could be overestimated since these cases are not individualized among stages IIB in most series.

To date, there is not enough robust data to determine whether chemotherapy alone or ABVD-based combined modality is the better treatment option for this subset of patients. PET-tailored[4,6-9] strategies have demonstrated a better benefit/risk ratio for all stages since they decrease acute and late toxicities without impairing tumor control. Whether PET-guided strategies could influence the choice of treatment in this population remains to be determined. In order to compare the outcomes of high-risk IIB HL patients treated with a combined modality treatment or as advanced stage disease, we retrospectively analyzed patients enrolled in two prospective phase III trials, H10 and AHL2011, conducted by LYSA, EORTC and FIL.

Methods

Patients and study design

2,748 patients with newly diagnosed, biopsy-proven classical HL according to the World Health Organization 2008 classification[10] were enrolled in two multi-center randomized trials, dedicated to early stage (H10, n=1,925)[3,4] and advanced stage HL (AHL2011, n=823).[7]

Briefly, the H10 trial enrolled patients aged 15 to 70 years, both favorable (F) and unfavorable (U) patients according to EORTC criteria.[3,4] The AHL2011 trial[7] enrolled patients aged 16 to 60 years who had Ann Arbor stage III, IV or IIB with a mediastinum-to-thorax ≥0.33 or extranodal localization. The complete eligibility criteria and strategies of treatment tailored by interim PET in both trials are presented in the H10[3,4] and AHL2011[7] trials.

The present study enrolled patients from the H10 or AHL2011 trial with high-risk IIB HL according to the GHSG stratification which is used by several groups worldwide[2] (Ann Arbor stage IIB with mediastinum-to-thorax [M/T] ratio ≥0.33 or extranodal localization), with available baseline PET (PET0) and after two cycles of chemotherapy images (PET2) and treated in LYSA centers as metabolic tumor volume (MTV) PET calculation was only done in LYSA patients (Figure 1). Thus, in the H10 study, PET0 and PET2 images were not available for 182 patients.

Both studies were carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. All patients provided written informed consent before study inclusion. The H10 and AHL2011 studies were registered at clinicaltrials gov. Identifier: NCT00433433 and NCT01358747.

Positron emission/computerized tomography acquisition and analysis

PET0 acquisition was performed before any treatment. The details of instructions and quality criteria are presented in the H10 and AHL trials.

PET0 images were centrally reviewed by three readers (SK, ASC, MM) blinded to medical information, and analyzed using the free open-source software, Beth Israel Plugin for Fiji (http://petctviewer.org).

Pathological uptake was defined by an increase uptake of 18-FDG over physiological background. Total metabolic tumor volume (TMTV) at baseline was calculated using a 41% SUV_{max} cutoff for each lesion.[11] In this study, all PET2 responses were centrally evaluated using the Deauville score (DS)[12,13] and PET positivity was defined according to the criteria used in the AHL2011 study[7] considered more reproducible with better positive predictive value than classic DS. Indeed, interim PET with DS 5 or 4 with SUV_{max} of the residual mass greater than 140% of the liver background were considered positive in the AHL study based on previous data showing the better reproducibility and accuracy of this threshold compared to visual analysis.[14] So, in the H10 study, interim PET were re-analyzed accordingly.

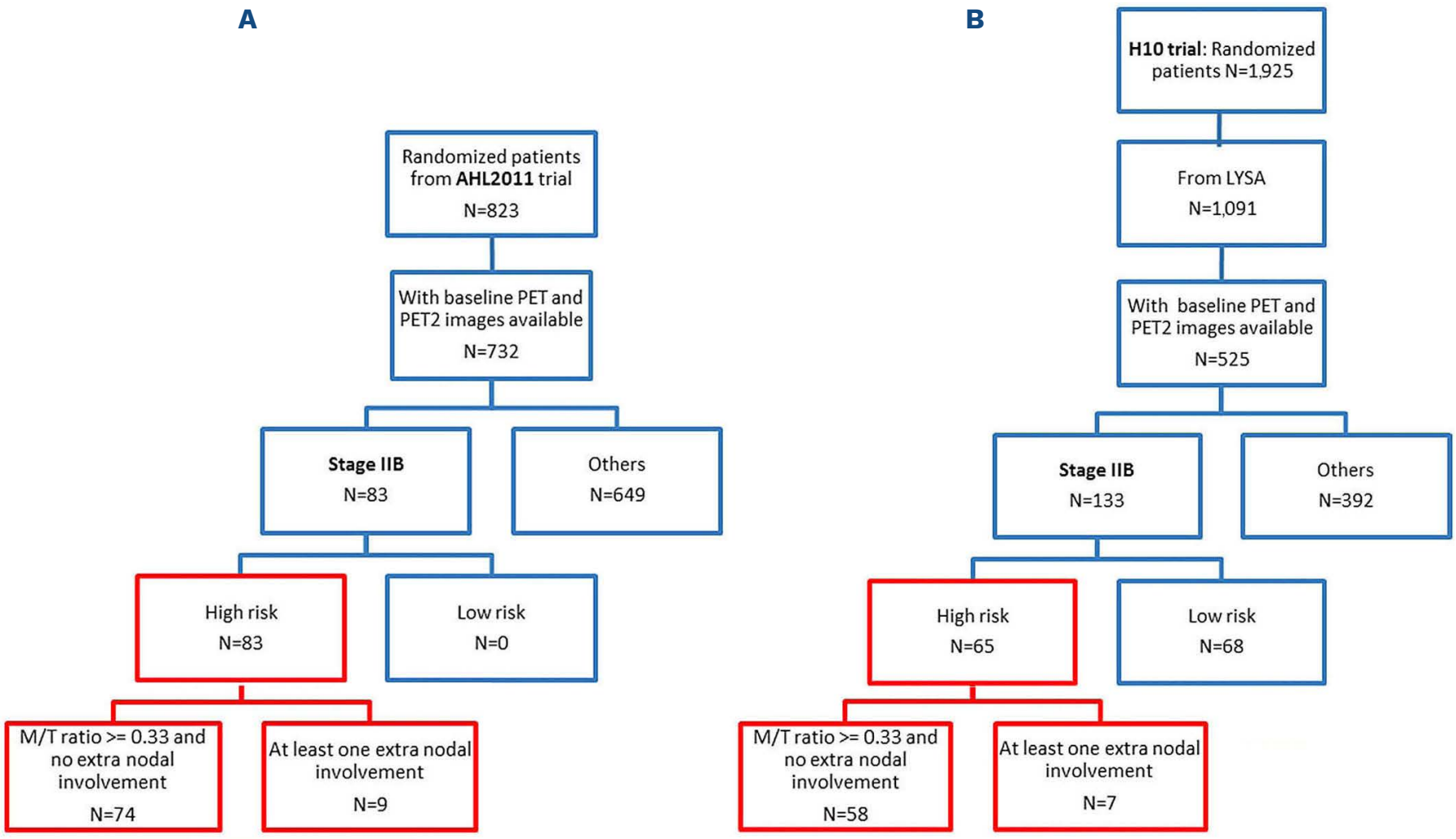

Figure 1. CONSORT diagram for selection of eligible patients. On the left, patients included in the AHL2011 trial and on the right included in the H10 trial. M/T: mediastinal/thoracic ratio; PET: positron emission tomograpy; PET2: PET after 2 cycles of chemotherapy.

Statistics

We assessed the efficacy of various treatment strategies, and compared the two trials in terms of interim PET response, progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from randomization to first progression, relapse or death from any cause or last follow-up. OS was defined as the time from randomization to death from any cause or last follow-up. The data cutoff for the analyses presented here was October 31st 2017, for the AHL trial and February 5th 2018, for the H10 trial. PFS and OS were analyzed on an intention-to-treat basis. Survival estimates with 95% confidence intervals (CI) were calculated with the Kaplan-Meier method. The survival distributions were compared with stratified log-rank tests according to the study, and Cox proportional hazard regression models were used to estimate hazard ratios (HR) and associated 95% CI. Multivariate analyses were conducted using a Cox proportional hazard model and including 120 patients due to missing index prognosis scoring (IPS) in 28 patients.

Three different approaches (X tile analysis,[15] receiver-operating characteristic analysis, and using the median) were used to define the optimal cutoff for survival prediction of TMTV.

Differences between groups were significant if *P*-values were less than 0.05. Population characteristics were compared using Fisher's exact test or X^2 test for discrete variables and *t*-test or Mann-Withney test for continous variables.

All analyses were produced with SAS software (version 9.3).

Results

Patients

Among the 1,091 patients assigned to the H10 trial by LYSA centers, 133 patients (12%) were enrolled with IIB staging. Among those patients, 65 (6%) met high-risk criteria: 58 had a M/T ratio ≥ 0.33 and the two others had at least one extra nodal involvement (Figure 1A). Among the 823 patients enrolled in the AHL2011 trial, 83 patients (10%) had stage IIB (all with high-risk criteria), including 74 with M/T ratio ≥0.33 and nine with at least one extra nodal involvement (Figure 1B). In the whole cohort of 148 patients (Table 1), the median age at baseline was 27 years (range, 16-59 years) and 53% (n=79) of patients were male. In the 120 of 148 patients with available data, the IPS was high (at least 3 or higher) in 43 (29%) of them. Baseline median TMTV was 155.5 mL (range, 8.3-782.9 mL; interquartile range [IQR], 97.3-256.2).

The patient characteristics were well-balanced in both studies except for two parameters. IPS was more fre-

Table 1. Patient characteristics.

	AHL2011 study N=83	H10 study N=65	All N=148	Test
Sex, N (%)				Chi-2, *P*=0.059
Male	50 (60%)	29 (45%)	79 (53%)	
Female	33 (40%)	36 (55%)	69 (47%)	
Age in years				*t*-test, *P*=0.119
Median (range)	26 (16-58)	29 (17-59)	27 (16-59)	
IPS group, N (%)				Chi-2, *P*<0.001
0-2	51 (61%)	26 (40%)	77 (52%)	
≥ 3	32 (39%)	11 (17%)	43 (29%)	
Unknown	0 (0%)	28 (43%)	28 (19%)	
Baseline TMTV (mL)				*t*-test, *P*=0.043
Median (range)	165.6 (43.6-782.9)	147 (8.3-572.3)	155.5 (8.3-782.9)	
IQR	121.7-294.9	121.7-294.9	121.7-294.9	
Arm according to randomization, N (%)				Chi-2, *P*=0.837
Standard	41 (49%)	31 (48%)	72 (49%)	
Experimental	42 (51%)	34 (52%)	76 (51%)	

IPS: international prognostic score; TMTV: total metabolic tumor volume; IQR: interquartile range.

quently unfavorable (IPS 3 or higher: 39% *vs.* 17%; *P*<0.001) and TMTV was significantly higher (165.6 mL *vs.* 147 mL; *P*=0.043) in AHL patients (Table 1; *Online Supplementary Figure S1*).

In the cohort as a whole, 72 patients (49%) were assigned to standard arms, while 76 (51%) were randomized to experimental arms and the treatment actually received are detailed in the *Online Supplementary Table S1*: 92 (62%) patients received a treatment including at least two cycles of escBEACOPP, including 51 (34%) patients treated with six cycles, 32 (22%) who received two cycles of upfront escBEACOPP followed by four cycles of ABVD and nine (6%) patients who received two cycles of escBEACOPP after two cycles of ABVD and followed by INRT. Overall, 47 (32%) patients received radiotherapy.

Responses and outcomes

Centrally reviewed PET2 was negative in 126 (85.1%) patients, including 67 of 83 (80.7%) in the AHL2011 study and 59 of 65 (90.8%) in the H10 study. Among the six positive PET2 patients in the H10 study, five (83%) had a DS5 while one DS5 was observed among 16 (6%) positive PET2 patients in the AHL study (*Online Supplementary Table S2*).

With a median follow-up of 4.1 years (95% CI: 3.9-4.4), a total of 17 PFS events occured: nine patients relapsed and one patient died from causes unrelated to HL in the AHL2011 trial, and seven patients relapsed in the H10 trial. Median PFS and OS were not reached in the whole cohort or either treatment group with the current follow-up. Overall, 4-year PFS was 88.0% (95% CI: 81.2-92.4) and by study 87.0% (95% CI: 76.8-92.9) and 89.2% (95% CI: 78.7-94.7) in AHL2011 and in H10, respectively (Figure 2). Five deaths occurred (3.4%): one unrelated to HL in AHL2011, and four in H10, among whom three were due to HL progression and one due to acute cardiorespiratory failure not related to lymphoma. Four-year OS was 96.1% (95%: CI 90.7-98.4) in the whole cohort, and 98.0% (95% CI: 86.6-99.7) *versus* 93.6% (95% CI: 84.4-97.6) in the AHL2011 and in H10 groups, respectively (Figure 2).

Relapses

The characteristics of the 16 patients who relapsed are detailed in the Table 2, nine of them were treated in the AHL2011 trial and seven in the H10 trial including three patients who received ABVD only.

Eleven of 16 relapses occurred in the mediastinum, one of four (25%) patients who received radiation *versus* ten of 12 (83%) who did not. Therefore, 7.4% of patients relapsed in our series, compared with 126 (4.6%) among the 2,748 pooled patients of the two trials. Among the 11 patients with progression in the mediastinum, only two (18.2%) had lesions outside the mediastinum.

Baseline prognosis factors

TMTV, either as a continuous variable or with a 155 mL threshold corresponding to the TMTV median value, was found to influence PFS estimates (HR=3.35; 95% CI: 1.093-10.285, *P*=0.035) (Figure 3) in univariate analysis. In the multivariate analysis, TMTV as a continuous variable was an independent predictor of PFS (*P*=0.048).

The cutoff sensitivity was 76% in the whole cohort, and 80% and 71% in AHL2011 and in H10 trials, respectively (AHL2011 area under the curve [AUC]=0.711, H10 AUC=0.632). The specificity of this cutoff for PFS was 52%. Among the 16 patients who experienced disease progression, 13 (81%) had a baseline TMTV ≥155 mL.

In univariate analysis (Table 2), no other baseline parameter was found to impact PFS estimates though there was a trend towards lower PFS in patients with high IPS. Indeed, among all evaluable patients (n=120) in the cohort, 4-year

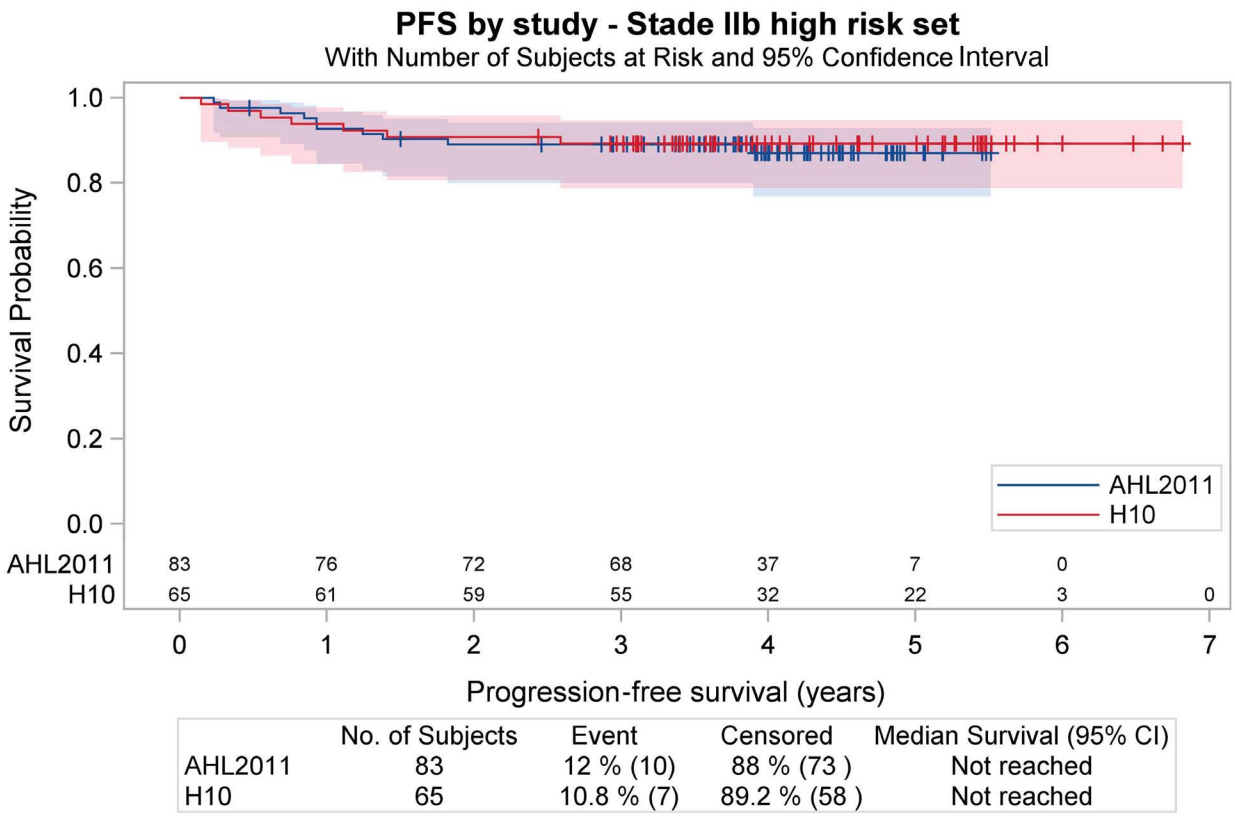

Figure 2. Progression-free survival according to the study assigned. PFS: progression free survival; CI: confidence interval.

PFS was 93.5% (95% CI: 85.5-97.2) for patients with IPS 0-2 *versus* 79.6% (95% CI: 62.8-89.4) for those with high IPS 3-7 (HR=2.89; *P*=0.064) (Table 2; *Online Supplementary Figure S2*). High IPS (≥3) was associated with a higher median TMTV (212.7 mL) than low IPS patients (148 mL). High TMTV was observed in 43% of the IPS ≥3 group and 34% in the IPS <3 group. To note, patients with missing IPS had similar PFS and inclusion in these analyses did not modify results.

Impact of treatment and positron emission tomography after two cycles of chemotherapy response on patient's outcome

In the whole cohort, patients with positive PET2 using modified DS assessment (n=20, 14% with 14 in AHL2011 and 6 in H10) had shorter PFS, than those with negative PET2 (4-year PFS: 91.5% [95% CI: 84.6–95.4] *vs*. 67.2% [95% CI: 53.1-82.8]; HR=0.181 [95% CI: 0.066-0.5]; *P*=0.001). PET2 was also centrally assessed using standard DS. PFS was still significantly influenced by stantard DS (4-year PFS in 1/2/3 *vs*. 4/5: 91.9% [95% CI: 84.2–96] *vs*. 76.5% [95% CI: 59.7-87]; HR=0.263 [95% CI: 0.098-0.706]; *P*=0.0046), but modified DS better discrimates populations of patients with different outcome and was used for further analysis.

PFS was similar in patients who did or did not receive esc-BEACOPP (HR=1.12, 95% CI: 0.42-3.05; *P*=0.81) and those who did (n=47) or did not receive (n=101) radiotherapy (HR=0.64, 95% CI: 0.21-1.95; *P*=0.42).

Overall, 4-year PFS was 63.8% (95% CI: 38.6-80.8) *versus* 91.6% (95% CI: 84.8-95.5) (Figure 3B; Table 2).

Baseline total metabolic tumor volume and positron emission tomography after two cycles of chemotherapy response predict patient outcome

In multivariate analysis with IPS, TMTV and PET2 as covariates, only baseline TMTV (HR=4.94; 95% CI: 1.05-23.16; *P*=0.043) and PET2 result (HR=3.49; *P*=0.031) were statistically independant predictors of PFS (Table 2). The TMTV as a continuous variable was also an independent predictor of PFS (*P*=0.048).

The combination of TMTV and PET2 results can be used to stratify patients in thre risk categories (Figure 3C). The group of patients with baseline TMTV ≥155 mL and positive PET2 (n=13) had the poorest PFS (46.2%), while patients with either one or none of the two parameters had PFS in more 90% (4-year PFS: 91.3 and 92.7 respectively). The HR of these combined factors (baseline TMTV ≥155 mL and positive PET2) *versus* one of them (either baseline TMTV ≥155 mL or positive PET2) was 13.356 (95% CI: 3.8-45.8; *P*<0.001).

Lastly, patients with high TMTV, high IPS and positive PET2 were scarce (4%, n=6) but three of them relapsed, while none of the patients without these factors relapsed and only 11.2% of patients with one or two of these factors relapsed.

Discussion

To the best of our knowledge, this is the first report to compare treatment strategies in high-risk stage IIB patients, with a large mediastinal mass or extranodal lesions according to the GHSG stratification system. No previous analysis of bulky stage IIB patients was previously reported. The CALGB study[16] which enrolled bulky stages I and II patients treated with ABVD followed by a PET-driven radiotherapy did not present data separately for patients with stage IIB. Similarly, the RATHL study enrolled 42% of stage II patients but no data was available in stage IIB patients.

Table 2. Univariate and multivariate analysis of prognostic factors associated with progression-free survival.

	Number of patients (%)	4-year progression-free survival, %	Stratified Logrank test (1)	Univariate analysis (Cox model) (1)		Multivariate analysis (Cox model)	
			P-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
IPS							
High IPS (IPS ≥ 3)	43 (29)	79.6	0.22	2.23	0.15		
Low IPS (IPS 0-2)	77 (52)	93.5		(0.6-8.32)			
Unknown	28 (19%)	85.6					
Baseline TMTV							
High TMTV (≥ 155)	72 (49)	82.9	0.025	3.37	0.035	4.94	0.043
Low TMTV (<155)	76 (51)	93.3		(1.09-10.37)		(1.05-23.16)	
Centrally reviewed PET2							
Positive	20 (14)	63.8	<0.0001	6.26	0.0003	3.49	0.031
Negative	128 (86)	91.6		(2.29-17.07)		(1.12-10.88)	

HR: hazard ratio; TMTV: total metabolic tumor volume, DS: Deauville score; IPS: IPS: international prognostic score: CI: confidence interval; PET2: positron emission tomography after 2 cycles of chemotherapy. (1) Cox regression model stratified by trial with fixed effects (as well as univariate Cox model and log-rank test)

Treatment strategies, including upfront ABVD chemotherapy (RATHL study,[8] H10 trial[3,4]) or upfront BEACOPP (AHL2011[7]) with no radiotherapy, seem to provide similar efficacy. However, compared with patients included in the H10 study, patients enrolled in the AHL2011 study had more severe disease at baseline with both more frequent high IPS and TMTV ≥155 mL and despite more unfavorable upfront profile in AHL patients, a *post hoc* analyses showed a similar outcome between H10 and AHL2011 patients, suggesting that the upfront dose intensity of chemotherapy delivered when using escBEACOPP is able to reverse the unfavorable prognosis value of baseline factors. However, because of the low number of patients and events in each treatment subgroup, we are unable to conclude definitively, and validation is required in a larger series. Additionally, in our study some patients with unfavorable risk factors experienced relapse even after escBEACOPP, suggesting there is an unmet medical need for these patients. While CALGB and RATHL studies confirm the reliability of PET-guided strategy (radiotherapy in CALGB study and chemo regimen in RATHL) no data on the baseline TMTV characteristics were available allowing to compare these results with ours. As underlined in the CALGB study,[16] one caveat for these limited staged patients is that bulk mass is defined differently according to groups in the world. In order to overcome this issue, the TMTV measure could be a better indicator in the very bulky mass and be helpful to the generalizability of better strategies of treatment. In line with this objective, we demonstrated in this study that baseline TMTV ≥155 mL was associated with an unfavorable prognostic impact independently of treatment strategy. This TMTV threshold is relatively in line with values reported in the literature for HL[17,18,19] (ranging from 147 to 313 mL). It is worth noting that the threshold of 147 mL[17] was determined from H10 patients with stage I-II. Also, all of the cutoffs described in study AHL2011 and H10 and in the whole cohort indicate that high baseline TMTV predicts significantly worse PFS. Indeed, TMTV reflects both the 3-dimensional tumor burden and metabolic activity, and provides additional prognostic information beyond classical risk, including the unidimensional measurement of tumor bulky such as M/T ratio.[19] In the present series, all patients (with available IPS) who experienced relapse had at least one of the baseline risk factors either TMTV ≥155 mL or IPS >3. Early PET response remains an independent prognostic factor in bulky mediastinal HL. However, less than half of relapses occured in positive PET2 patients, and other parameters including TMTV and IPS are required to better stratify. PET radiomics could also help to predict outcomes in patients with mediastinal HL.[20]

HL is a radiosensitive disease, and omitting radiotherapy as consolidation treatment in early stage HL was associated with a higher risk of treatment failure in patients responding to upfront ABVD.[6] However, omitting radiation therapy consolidation is possible in patients achieving complete metabolic response after two cycles of escBEACOPP plus two cycles of ABVD without loss of tumor control[21] in unfavorable localized HL. In the present study, patients treated with upfront escBEACOPP with neither radiotherapy consolidation nor radiotherapy after relapse had outcomes similar to patients receiving radiotherapy despite a more unfavorable profile at baseline. In addition, four (8.5%) of the 47 patients who received radiation therapy relapsed, including three relapses outside of the mediastinum, compared to 12 (11.8%) of the 101 of patients who received only chemotherapy, suggesting that radiation ther-

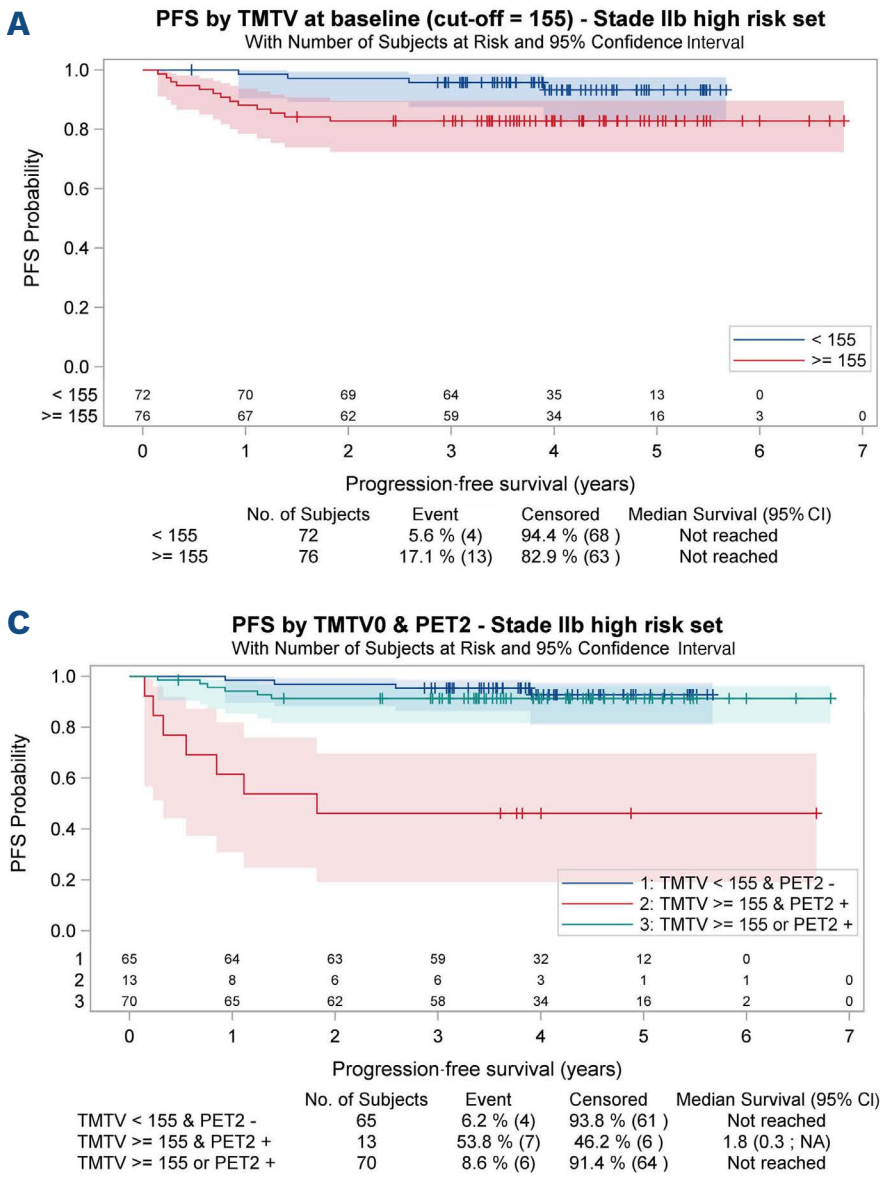

Figure 3. Progression-free survival according to total metabolic tumor volume and positron emission tomography after two cycles of chemotherpy response. (A) Progression-free survival (PFS) according to total metabolic tumor volume (TMTV) with a cutoff of 155 mL, (B) according to positron emission tomography results after 2 cycles of chemotherpay (PET2) assessed with modified Deauville score (see Methods) and (C) according to the TMTV and PET2 result combination.

apy had probably little effect on tumor control as shown in the unfavorable group of the H10 trial.[4] In the HD15 trial, a relapse was recorded in 28 of 152 advanced HL patients with a PET-positive residual mass at the end of chemotherapy and with documented radiotherapy, of which seven relapses occurred outside of the irradiated sites.[22] In high-risk stage IIB patients, the fields targeted by radiotherapy are usually large, even in case of involved node radiotherapy, as most patients have bulky mediastinal mass, leading to an increased risk of toxicity in non-targeted organs such as the heart or breast. In terms of benefit-risk balance, our results do not allow to determine if a radiotherapy-free strategy using more intense upfront chemotherapy regimen such as escBEACOPP might be more suitable in these patients with bulky mass allowing to avoid long-term radiotherapy side effects without loss of tumor control or if radiotherapy is mandatory to decrease the risk of relapse.

The present study has several limitations. Firstly, even though we analyzed patients enrolled in two prospective trials, this is a retrospective analysis which involves inevitable biases: IPS was not available for 19% of patients of H10 study because it was not designed or required for baseline stratification of patients with early stage disease. Secondly, patients with high-risk stage IIB were quite rare representing 11% of patients included in AHL2011 and 6% in patients included in H10 studies. There was also a low rate of treatment failure, limiting the power of statistical analysis. However, few studies have focused on this subset of patients in the literature, and a randomized study cannot easily be conducted in such a limited population. Altogether, our results stemming from patients enrolled in two randomized trials with different treatment options are important to demonstrate that patients with high risk stage IIB HL could be treated either by combined modalities or with upfront escBEACOPP without radiotherapy consolidation. While the optimal treatment for patients with very bulky mass remains unclear, the TMTV seems a better indicator to stratify patients at diagnosis and very helpful to the decision. The potential benefit of escBEACOPP in patients high TMTV stage IIB has to be further investigated in larger series.

Disclosures

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Contributions

CR, MA, MM, ASC and OC developed and designed the study and collected and assembled the data. All authors analyzed and interpreted the data, wrote the manuscript, gave their final approval of the manuscript and are accountable for all aspects of work.

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Data-sharing statement

The original data cannot be shared due to the limited access to data bases.

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