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Combined prognostic value of absolute lymphocyte/monocyte ratio in peripheral blood and interim PET/CT results in Hodgkin lymphoma

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Abstract Decreased absolute lymphocyte/monocyte ratio (LMR) in peripheral blood has been reported as an unfavorable prognostic marker in Hodgkin lymphoma. We aimed to investigate whether combining LMR and interim PET/CT scan result (PET2) confers stronger prognostic value than PET2 alone. 121 HL patients were investigated. LMR was calculated from a blood sample taken at the time of diagnosis. PET2 was carried out after the second chemotherapy cycle. Survival was calculated using the Kaplan–Meier method and significance was determined by log-rank test. Effect of variants on survival results was examined using univariate and multivariate analyses. Best LMR cut-off value was determined by receiver operating characteristic (ROC) curve. Best LMR cut-off value was 2.11 in the case of our patients (LMR >2.11: favorable, LMR ≤2.11: unfavorable). Overall and progression-free survivals (OS/PFS) were significantly worse both in lower LMR (≤2.11) (OS: $P = 0.041$, PFS: $P = 0.044$) and PET2 positive groups (OS: $P < 0.001$, PFS: $P < 0.001$). In PET2 positive patient group ($n = 32$) the low LMR result meant a significantly worse OS (0.030) and PFS (0.001). Both LMR and PET2 proved to be independent prognostic factors on multivariate analysis, and strengthened each other's effect.

Introduction

The 2-[^{18}F] fluoro-deoxy-D-glucose positron emission tomography combined with helical multidetector computed tomography (PET/CT) plays an important role in the treatment of Hodgkin lymphoma (HL). It is a well known fact that in advanced-stage HL patients, the interim PET/CT (PET2) carried out after the second cycle of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) has a higher prognostic value, compared to traditionally used IPS (International Prognostic Score) [1]. During the recent years, it has been proved that negative predictive value (NPV) of PET2 examination is excellent, higher than 90 %, but its positive predictive value (PPV) is not strong enough, usually between 50 and 70 % [2, 3]. Although some clinical studies are in progress aiming to investigate whether early treatment modification based on the PET2 result improves survival in HL, but on one hand these data are less known yet, and on the other hand it would also be desirable, if treatment intensification was indeed carried out in those patients who are at high risk of primary refractory disease or early progression/relapse of HL.

According to latest literature data we can say that several biological markers may play a role in the prognosis of HL. Elevated tumor-associated macrophage (TAM) ratio in lesional tissues is associated with a worse overall survival (OS) [4]. TAMs can be investigated by gene expression profile analysis and subsequent immunohistochemical staining for CD68, CD163, but these methods are not used as routine diagnostic procedures yet. These macrophages are originated from circulating monocytes and migrate to

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the lymph nodes due to the effect of soluble chemotactic factors derived from the tumor [5]. Prognostic value of low absolute lymphocyte count of peripheral blood is well established, we used it as an independent prognostic factor in IPS as well [6]. Based on these data some workgroups investigated the prognostic value of absolute lymphocyte/monocyte ratio (LMR) of peripheral blood in HL. These studies have proved that lower LMR is associated with unfavorable survival results [4, 5, 7]. Considering all the above in our work we studied whether the lower positive predictive value of PET2 examination can be improved using an easily accessible biological marker, the LMR.

Patients and methods

Patients

A total of 121 patients, newly diagnosed with HL between 2007 and 2013, were enrolled into the study from the North-Eastern Region of Hungary (Debrecen, Miskolc, Nyíregyháza, Szolnok). Histological diagnosis was made according to the REAL/WHO classification. Patients did not receive former treatment, they were not treated with immunosuppressive medications and immunodeficiency was not present. Clinical data of patients were available from the medical records. The study was approved by the local ethics committee. As the whole study was a retrospective, observational trial, informed consent was not obtained.

Clinical endpoint

Primary endpoint of the trial was to specify, whether positive predictive value of PET2 examination can be increased by using peripheral blood LMR. We analyzed the influence of LMR and PET2 examinations and their combined effects on the overall and progression-free survival (OS, PFS) as secondary endpoints.

Method

Absolute lymphocyte/monocyte ratio of peripheral blood was calculated from the complete blood cell count measured at the time HL was diagnosed, before the first ABVD treatment. PET2 examination was carried out after the second cycle of chemotherapy between days 11 and 14. The examination was the combination of whole body ^{18}F-fluoro-deoxy-D-glucose positron emission tomography and low-dose CT scan in each case. Baseline PET/CT was also carried out in case of every patient for staging purposes and interim result was compared to this. The 5-point Deauville criteria [8] were used during evaluation.

A score of 1–3 was considered to be negative and 4 or 5 to be positive.

Response to therapy and survival

Determination of response to therapy, overall survival, progression-free survival and time to progression was carried out according to the International Harmonization Project on Lymphoma guideline [9].

Statistical analysis

Independent t test was used to examine homogeneity of the samples, survivals were calculated according to the Kaplan–Meier method. The curves were compared for statistical significance using log-rank testing.

The effect of variants on survivals was examined using the univariate and multivariate analysis of Cox proportional hazard model (forward stepwise method). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of the LMR. The binary clinical outcome (death or survival) was determined 5 years after the diagnosis. In case of patients with a longer follow-up period their state was determined at the 5-year time point (alive/censored or death). In case of patients with a shorter follow-up time, the outcome was determined when the patient died. Categorical variables were compared using the Chi-square test (χ^2). Statistical data analysis was performed with IBM SPSS Statistics 20 software. P values less than 0.05 were considered statistically significant. Sensitivity, specificity, negative and positive predictive values were calculated according to the known mathematical methods.

Results

Patients

The results of 121 patients were analyzed in this study. The mean follow-up time was 47.52 months (11–80 months). Detailed clinical data of patients are presented in Table 1. Staging was performed according to the Cotswolds modification of the Ann Arbor staging system. Stages IA–IIB were considered to be early-stage and IIIA–IIIB stages as advanced-stage disease. During the treatment period patients received either chemotherapy alone (ChT, $n = 46$) or combined chemo-radiotherapy (CMT, $n = 76$: chemotherapy: ABVD + involved field irradiation). Combined modality treatment was applied as consolidation therapy in case of each early-stage patient and in advanced-stage disease, when bulky tumor was presented at the time of diagnosis. While the gender, the stage of the disease or the

Table 1 Clinical characteristics of 123 classical Hodgkin lymphoma (cHL) patients

| Patient characteristics ($n = 121$)	
Mean age (ranges, years)	36.7 (17–79)
Gender (male/female)	60/61
Histology (cHL) (%)	
NS	56 (46.4)
MC	33 (27.4)
LR	25 (20.2)
LD	1 (0.8)
ND	6 (5)
Stage (%)	
Early IA–IIB	65 (53.7)
Advanced IIIA–IVB	56 (46.3)
B symptoms are present/absent	64/57
Bulky tumor present/absent	43/78
Treatment	
ABVD 6 cycles	32
ABVD 8 cycles	14
ABVD 4 cycles + 30 Gy RT	33
ABVD 6 cycles + 30 Gy RT	32
ABVD 6 cycles + 36 Gy RT	11

NS nodular sclerosis, *MC* mixed cellularity, *LR* lymphocyte rich, *LD* lymphocyte depletion, *ND* not differentiated, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *RT* radiotherapy

presence of bulky tumor had not had influence on the survivals, then the younger age increased the overall survival (OS <35 years: 95.2 %, ≥35 years 73.2 %, $P = 0.008$) and the combined modality treatment improved the progression-free survival (PFS ChT: 67.4 %, CMT: 84 %, $P = 0.014$, it has no impact on the OS: 81.3 vs. 87.9 %, $P = 0.454$) of our patients.

Thirteen patients died during the follow-up period (10.6 %). Three of them died from secondary tumor and ten patients died because of the progression of HL or due to infections associated with repeated treatments.

Lymphocyte/monocyte ratio

As the measurements of peripheral blood samples were not carried out in the same laboratory, we compared these values with each other (university laboratory $n = 85$, three hospital laboratories $n = 36$). We found that both absolute lymphocyte counts and absolute monocyte counts were higher in hospital laboratories, but regarding the ratios results were homogeneous. We could not determinate statistically significant cut-off value neither in the case of absolute lymphocyte counts, nor in the case of absolute monocyte counts using the ROC curve, maybe due to the differences in measurement results. The sample was homogeneous regarding LMR
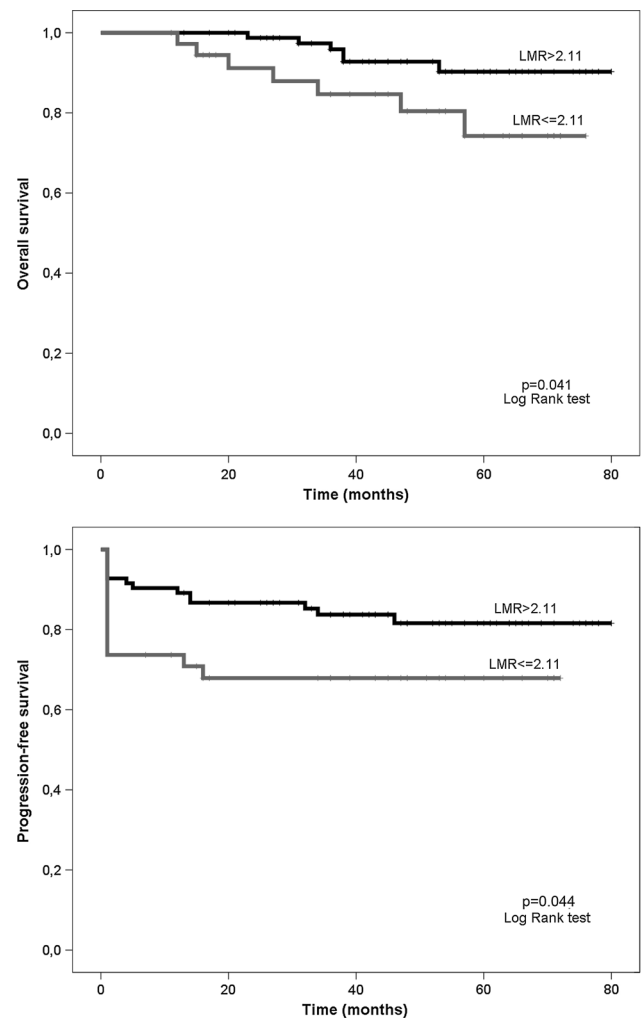
Fig. 1 Overall and progression-free survival depending on the absolute lymphocyte/monocyte ratio of peripheral blood measured at the time of diagnosis

and using the ROC curve the cut-off value was 2.11. Values ≤2.11 were considered to be unfavorable and values >2.11 as favorable prognostic markers. In case of a lower LMR both the overall and the progression-free survival were significantly worse (OS: 74.3 vs. 90.3 %, $P = 0.044$; PFS: 67.2 vs. 81.6 %, $P = 0.044$) (Fig. 1). LMR proved to be an independent prognostic factor regarding progression-free and overall survival also using multivariate analysis; however, it was not an independent prognostic factor with univariate analysis (Table 2).

Interim PET/CT scan (PET2)

Both overall and progression-free survival rates showed significant differences according to the interim PET/CT scan results performed after the second completed ABVD cycle (Fig. 2). Survival rates of PET2 negative patients

Table 2 Examination of prognostic factors regarding overall (OS) and progression-free survival (PFS) of our patients with Hodgkin lymphoma

	OS ($n = 121$)			PFS ($n = 121$)		
	HR	95 % CI	P	HR	95 % CI	P
Univariate analysis						
LMR (≤ 2.11)	2.96	0.99–8.80	0.052	2.11	0.97–4.56	0.059
PET2 (positive)	6.93	2.13–22.54	**0.010**	11.70	4.66–29.31	**<0.001**
Age (≥ 35 years)	4.87	1.34–17.69	**0.016**	1.51	0.70–3.26	0.294
Stage (III–IV)	2.01	0.66–6.15	0.220	1.98	0.89–4.37	0.090
Gender (female)	1.16	0.39–3.46	0.786	1.36	0.62–2.96	0.438
B-symptom (present)	1.34	0.44–4.10	0.609	2.54	1.07–6.04	**0.036**
Bulky (present)	0.85	0.26–2.75	0.782	0.96	0.43–2.16	0.930
Treatment (chemotherapy)	1.51	0.51–4.50	0.457	2.51	1.15–5.47	0.021
Multivariate analysis						
LMR (≤ 2.11)	5.57	1.53–20.25	**0.003**	4.39	1.87–10.27	**0.001**
PET2 (positive)	11.51	3.14–42.86	**<0.001**	17.74	6.61–47.57	**<0.001**

Bold values are significant

LMR peripheral blood absolute lymphocyte/monocyte ratio, *PET2* interim PET/CT examination, *HR* hazard ratio, *CI* confidence interval, *OS* overall survival, *PFS* progression-free survival
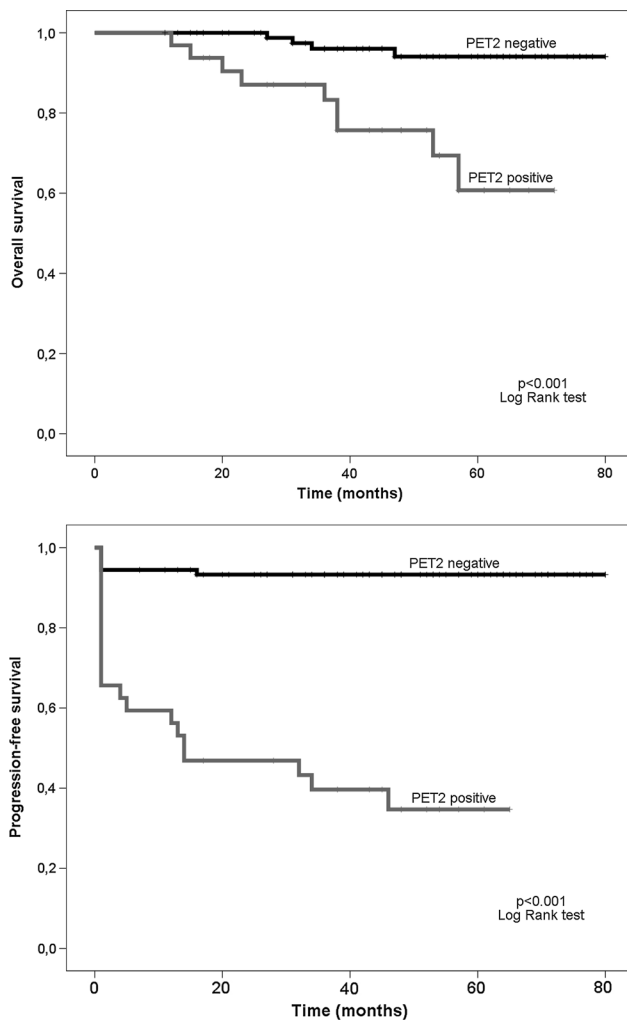
Fig. 2 Overall and progression-free survival depending on the results of interim PET/CT (PET2) carried out after the second completed ABVD treatment

were significantly better in both cases (OS: 94.1 vs. 60.7 %, $P < 0.001$; PFS: 93.2 vs. 34.7 %, $P < 0.001$). Sensitivity of the method was 76 % and specificity was 86 % regarding progression of HL (Table 3). There was no treatment modification based on PET2 result.

Combined evaluation of interim PET/CT and LMR

Thirty-two patients had positive findings on PET2 scan. Progression or relapse of the underlying disease was observed in 12 cases. Nine patients died out of these, all of them died of progressive disease or from treatment complications (infection). PET2 showed false positive results in 19 patients concerning progression of HL, with a positive predictive value (PPV) of only 59 %, while the negative predictive value (NPV) was 93.3 % (Table 3). We analyzed the overall and progression-free survival as well as a function of LMR values in case of the 32 PET2 positive patients. We found that lower LMR resulted in a significantly worse survival in both cases (OS 72.4 vs. 26.8 %, $P = 0.03$; PFS: 44.4 vs. 0 %) (Fig. 3). Among PET2 positive patients the positive predictive value of LMR regarding PFS was 100 %; therefore, progression of the underlying disease occurred in all patients with positive PET2 result and low LMR ($n = 7$). Six of them had primary refractory disease (Table 3). We investigated the impact of LMR on survival rates in PET2 negative patients ($n = 89$) as well. We found that within the patient group with good prognosis, higher LMR highlights a subgroup with even more favorable disease course (OS 98 vs. 87.2 %, $P = 0.076$; PFS 98.3 vs. 83.1 %, $P = 0.008$) (Fig. 3), and among the PET2 negative patients the NPV of LMR was slightly higher that the NPV of PET2 alone was (respectively: 98

Table 3 Prognostic value of peripheral blood absolute lymphocyte/monocyte ratio (LMR) and interim PET/CT examination (PET2) in our patients with Hodgkin lymphoma

	LMR	PET2	LMR	LMR
	OS all patients ($n = 121$)		PET2 positive ($n = 32$)	PET2 negative ($n = 89$)
Sensitivity (95 % CI)	0.54 (0.25–0.81)	0.69 (0.39–0.91)	0.44 (0.14–0.79)	0.75 (0.19–0.99)
Specificity (95 % CI)	0.71 (0.61–0.79)	0.79 (0.70–0.86)	0.86 (0.65–0.97)	0.67 (0.56–0.76)
PPV (95 % CI)	0.18 (0.78–0.34)	0.29 (0.14–0.48)	0.57 (0.19–0.90)	0.10 (0.02–0.25)
NPV (95 % CI)	0.93 (0.85–0.97)	0.95 (0.89–0.99)	0.79 (0.58–0.93)	0.98 (0.91–1.00)
	PFS all patients ($n = 121$)		PET2 positive ($n = 32$)	PET2 negative ($n = 89$)
Sensitivity (95 % CI)	0.48 (0.28–0.69)	0.76 (0.54–0.90)	0.35 (0.16–0.61)	0.83 (0.36–0.99)
Specificity (95 % CI)	0.73 (0.63–0.81)	0.86 (0.78–0.93)	1.00 (0.75–1.00)	0.69 (0.57–0.78)
PPV (95 % CI)	0.31 (0.17–0.48)	0.59 (0.41–0.76)	1.00 (0.59–1.00)	0.16 (0.05–0.33)
NPV (95 % CI)	0.84 (0.74–0.91)	0.93 (0.86–0.97)	0.52 (0.31–0.72)	0.98 (0.91–0.99)

Prognostic value of LMR among patients with positive and negative interim PET/CT result separately

CI confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *OS* overall survival, *PFS* progression-free survival
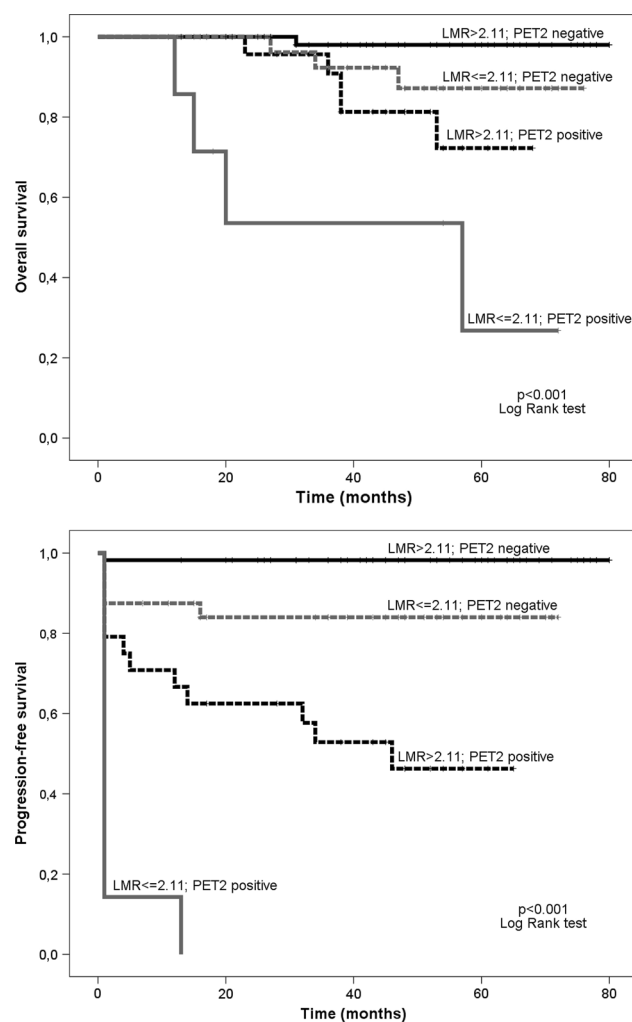
Fig. 3 Overall and progression-free survival depending on both the positive interim PET/CT (PET2) results and the absolute lymphocyte/monocyte ratio of peripheral blood

vs. 93 %) (Table 3). Univariate and multivariate analysis was used to examine the association between clinical variables and overall and progression-free survival (Table 2). With univariate analysis in terms of overall survival the PET2 result and the patient age ($</\geq 35$ years) proved to be an independent prognostic factor, while in terms of progression-free survival the PET2, B-symptom and the treatment type (combined modality treatment increased the PFS) were independent prognostic factors. However, with multivariate analysis only LMR and PET2 results remained to be independent prognostic marker.

Neither patient gender, nor clinical stage or bulky tumor, was found to be a prognostic factor.

Discussion

Breakthroughs in the treatment of Hodgkin lymphoma during the last 50 years transformed this disease to one of the success stories of hemato-oncology. One of the latest milestones of this journey is the application of interim PET/CT. Several studies have proved that PET2 result has a higher prognostic value compared to traditional clinical prognostic markers [1, 3, 10]. According to literature data it is known that sensitivity of this method is between 43 and 100 % and specificity varies between 67 and 100 % in terms of outcome of HL. Our data corresponds to this (Table 3) [10]. Several clinical studies are in progress based on the significant prognostic value of PET2, where treatment modification is a choice depending on the results of the interim examination [2, 3]. The method is known to have an excellent negative predictive value, above 90 %; however, its positive predictive value is significantly lower [3]. Therefore, treatment modification, intensification based on only

positive PET2 results may lead to overtreatment in most cases.

To achieve really personalized treatment for HL and much higher cure rate while avoiding undertreatment and overtreatment, we have to identify patients with highly favorable and unfavorable prognosis more effectively. Many papers have been published during the recent years concerning biomarkers that may prove as potentially useful prognostic factors. Activation-regulated chemokine/CCL17 (TARC) molecule [11, 12], the presence of tumor-associated macrophages (TAMs) [13, 14] in the tumor tissue and absolute lymphocyte/monocyte ratio (LMR) of peripheral blood [4, 5, 7] must be highlighted among them.

The detection of TAMs in Hodgkin lymphoma tissue samples can be performed using gene expression profile analysis and subsequent immunohistochemical staining for CD68, CD163. Increased relative tissue infiltration by macrophages correlates with poor prognosis. These tissue macrophages are derived from circulating monocytes. Therefore, it seemed logical to investigate peripheral blood absolute monocyte count (AMC) in terms of prognosis of HL. However, the prognostic value of higher AMC remains controversial. Although Porrata et al. [5] have confirmed that an AMC of 900 cells/μL or more is an indicator of an unfavorable survival, Koh et al. [4] could not prove that AMC is an independent prognostic factor. We could not establish such a cut-off value using the ROC curve among our patients that would give a significant difference. AMC did not have a prognostic value regarding OS and PFS despite using as a continuous variable.

While AMC may provide information about tumor microenvironment, absolute lymphocyte count (ALC) of peripheral blood can be related to the immunity of patients. ALC is well known from IPS as the prognostic factor of HL; lymphopenia predicts poor prognosis [6].

Combined evaluation of these two factors may characterize patient immunity and tumor microenvironment together as a biological system and correlate with the presence of tissue macrophages [4, 7]. Similarly to literature data [4, 5, 7, 15] with multivariate analysis LMR proved to be an independent prognostic factor in case of our patients as well regarding overall and progression-free survival (Fig. 1; Table 2). However, the fact is that different LMR cut-off values (1.1–2.9) can be found in various publications probably reflecting the differences of the populations [4, 5, 7, 15]. Our own value (cut-off: 2.11) is similar to the result of a Slovenian workgroup (2.2), also supporting regional/ethnical/economical differences. Although LMR itself holds prognostic value, the strength of it is worse compared to the prognostic value of PET2 (Tables 2, 3).

According to our present knowledge, the most appropriate method for the evaluation of the prognosis of HL is PET2 examination, though there are known limitations (low PPV) of it. The primary goal of our work was to examine whether the application of LMR is able to improve the positive predictive value of PET2 or not. The subgroup analysis carried out among the PET2 positive patients showed that low/unfavorable LMR clearly strengthens positive interim PET/CT result, as progression of HL occurred in each case of double positive patients (positive PET2, low LMR, $n = 7$). Primary refractory disease was confirmed in 6 patients. We did not have false positive results. On the other hand in the PET2 negative patient group we also could identify a sub-group with better prognosis using the LMR as an additive factor (Fig. 3). Among the 58 double negative patients only one had relapse of HL.

The combined effect of PET2 and LMR on the survival of HL patients is less known, we found only one publication in this topic [16]. Our data further confirmed that PET2 result indicates the outcome of HL the most. Nevertheless, the PPV was significantly lower compared to NPV in spite of using the internationally accepted and standardized, 5-point Deauville scale during evaluation. We highly agree with Porrata et al. [16] that in addition to PET2 examination, the application of LMR can be an easily available and cheap daily used method that may help us to identify those high-risk patients where early treatment modification/intensification (ABVD → BEACOPPesc, high dose therapy and early autologous transplantation, early administration of brentuximab vedotin, etc.) can be reasonable.

The weakness of our study is that we carried out a totally retrospective analysis with a fairly short follow-up period and low patient number. This may explain the higher standard deviations as well. We think that the main disadvantage of the method at present is the large scale of LMR cut-off values according to literature data (1.1–2.9) as it was suggested Romano et al. [17]. We do not have a clear explanation for this, but it would be useful to validate the cut-off value by a multicenter, international study examining a patient group with homogeneous treatment, if possible.

Conclusion

PET2 examination is the currently available best prognostic method in the treatment of HL patients and hopefully we will be increase the positive predictive value of this method in the near future to be able to early detect the primary refractory or early relapsing cases whose treatment can be a real challenge in the everyday practice. LMR seems to be a promising factor, which can help us to identify the worst prognosis patients but not only as an additive marker beside the PET2 examination.

Compliance with ethical standards

Conflict of interest   None of the authors have any competing interest in the manuscript.

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