End-of-treatment PET in early-stage Hodgkin lymphoma: valuable in addition to interim PET

Classic Hodgkin lymphoma (HL) is a B-cell malignancy that is associated with high rates of cure with front-line therapy.[1] Based on major clinical trials assessing treatment strategies adapted according to the findings of interim positron emission tomography (PET), the treatment paradigm for early-stage HL has evolved dramatically in the past decade.[2-4] While clinicians commonly rely on interim-PET to make treatment escalation or de-escalation decisions, an area that remains less well investigated is the role of end-of-treatment (EOT)-PET. Literature has questioned the necessity of EOT imaging, especially in interim-PET-negative individuals, and clinical trials are lacking.[5-7] There are limited real-world data assessing the prognostic value of EOT-PET and the importance of this scan in relation to interim-PET, especially in patients with early-stage disease. Thus, the primary objective of our study was to determine the utility of EOT-PET and its association with outcomes in early-stage HL. Our secondary objectives were to compare outcomes stratified by the interim-PET response and to assess treatment strategies used for EOT-positive disease.

Consecutive adult patients (≥18 years old) with previously untreated early-stage (IA-IIB) HL evaluated at the Mayo Clinic in Rochester, Arizona, and Florida from January 1, 2010 to December 31, 2020 were retrospectively assessed. Patients with missing clinical data, or EOT-PET unavailable for radiological review were excluded. This study was approved by the Mayo Clinic Institutional Review Board. Patients' data were collected through electronic chart review. Treatment modality was stratified into chemotherapy-alone or combined modality therapy. The number of treatment cycles was divided into four or fewer cycles, six cycles, and a novel consolidation group. EOT scans were identified as the first scan conducted after the completion of all frontline therapies (including consolidation therapies or radiotherapy). The standard at our institution is 6 weeks after chemotherapy completion, or 3 months after radiotherapy. Independent radiological review of PET2 scans (PET after 2 cycles of chemotherapy), end-of-chemotherapy (after the last chemotherapy cycle before radiotherapy), and EOT-PET scans was performed by a board-certified nuclear radiologist blinded to the patients' treatment and outcomes. The Deauville score (DS) was calculated for all scans: a DS >3 was used to characterize EOT-positive disease. Primary study endpoints were progression-free survival (PFS) and overall survival (OS). Cox-proportional hazard models were used to determine hazard ratios (HR). Survival analyses were conducted using the Kaplan-Meier method. Time-to-event analyses were based on the date of the PET scan to the date of the event. Progression events were determined from the date of a positive biopsy. A *P* value <0.05 was considered statistically significant. Analyses were conducted using SPSS 27, and BlueSky Ver 7.4.

Of 93 patients identified with early-stage HL (36 [39%] females, median age: 32 years [range, 18-78]), 83 (89%) patients were EOT-negative, and ten (11%) were EOT-positive. The patients' baseline and treatment-related characteristics are displayed in Table 1. Ninety-two (99%) patients received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or AVD (doxorubicin, vinblastine, dacarbazine)-based regimens, and one received a front-line combination of brentuximab vedotin and nivolumab. Ten (11%) patients received novel agent consolidation with single-agent nivolumab or brentuximab vedotin after front-line chemotherapy as part of clinical trials. All patients receiving combined modality therapy (n=38) had a plan for radiotherapy determined at baseline.

Comparing PET2 results with EOT outcomes, patients who were EOT-positive had a greater degree of PET2-positive disease (DS >3) compared to those who were EOT-negative (40% *vs.* 9%, *P*=0.006). Importantly, 60% of patients who were EOT-PET-positive were interim-PET-negative (DS ≤3). Among the patients receiving combined modality therapy (n=38), two (5%) were found to be EOT-positive. Prior to radiotherapy, 25 patients had an evaluable end-of-chemotherapy PET and three were found to be PET-positive, all of whom became negative on the EOT scan after radiotherapy. An end-of-chemotherapy scan was not available in the two patients who were positive at the EOT-PET after radiotherapy. No significant associations were observed between end-of-chemotherapy response (*P*=0.71) and EOT response in patients receiving combined modality therapy.

With a median follow-up of 48.1 months (95% confidence interval [95% CI]: 35.0-61.1), PFS was significantly reduced in patients who were EOT-positive compared to those who were EOT-negative (2-year PFS: 30% *vs*. 91%, respectively; *P*<0.001) (Figure 1). No significant association for OS was observed (*P*=0.34). Assessing hazard ratios, both PET2-positive (DS >3: HR=8.4 [95% CI: 2.9-24.3], *P*<0.001) and EOT-positive (DS >3: HR=15.1 [95% CI: 5.4-42.5], *P*<0.001) disease conferred an elevated risk of progression. Importantly, four (40%) of the ten patients with EOT-positive disease were found to have biopsy-proven progression despite a negative interim-PET. The inferior PFS associated with EOT-positive findings remained consistent regardless of the presence of disease bulk, or treatment modality. No PFS difference was

Table 1. Patients' baseline characteristics and differences between those positive and negative at the end-of-treatment positron emission tomography.

Characteristic	Whole cohort (N=93)	EOT-PET negative (N=83)	EOT-PET positive (N=10)	*P*
Age, years, median (range)	32 (18-78)	32 (18-78)	32 (22-49)	1.00
Female sex, N (%)	36 (38.7)	33 (39.8)	3 (30.0)	0.55
Histology, N (%)				
Nodular sclerosis	59 (63.4)	53 (63.9)	6 (60.0)	0.71
Mixed cellularity	4 (4.3)	3 (3.6)	1 (10.0)	
Lymphocyte-rich	4 (4.3)	4 (4.8)	0	
Classic	26 (28.0)	23 (27.7)	3 (30.0)	
Stage, N (%)				
IA	2 (2.2)	2 (2.4)	0	0.74
IB	0	0	0	
IIA	62 (66.7)	56 (67.5)	6 (60.0)	
IIB	29 (31.2)	25 (30.1)	4 (40.0)	
Prognostic factor, N (%)				
Unfavorable disease	62 (66.7)	55 (69.6)	7 (87.5)	0.29
Favorable disease	25 (26.9)	24 (30.4)	1 (12.5)	
Bulky disease (≥7 cm diameter), N (%)	35 (37.6)	30 (36.1)	5 (50.0)	0.39
Treatment strategy, N (%)				
CMT	38 (40.9)	36 (43.4)	2 (20.0)	0.16
Chemotherapy alone	55 (59.1)	47 (56.6)	8 (80.0)	
Treatment cycles, N (%)				
≤ 4 cycles	42 (45.2)	37 (44.6)	5 (50.0)	0.51
6 cycles	41 (44.1)	36 (43.4)	5 (50.0)	
Novel consolidation	10 (10.8)	10 (12.0)	0	
PET2 response, N (%)				
Negative (DS ≤2)	70 (81.4)	65 (85.5)	5 (50.0)	**0.007**
Positive (DS ≥3)	16 (18.6)	11 (14.5)	5 (50.0)	
Negative (DS ≤3)	75 (87.2)	69 (90.8)	6 (60.0)	**0.006**
Positive (DS >3)	11 (12.8)	7 (9.2)	4 (40.0)	
Survival outcomes, N (%)				
Relapsed/refractory disease	15 (16.2)			
Death	4 (4.3)			
HL-related death	2 (2.2)			

CMR: combined modality therapy; PET2: positron emission tomography scan after two cycles of chemotherapy; DS: Deauville score; HL: Hodgkin lymphoma. Statistically significant differences are shown in bold.

found comparing patients who received novel consolidation (n=10) to those who did not (n=83) (*P*=0.17). Excluding patients who received novel consolidation, those with EOT-positive disease continued to have significantly reduced PFS (median 0.2 months) compared to those with EOT-negative disease (median not reached) (*P*<0.001). In the small number of patients with EOT-PET DS 3 (n=4), a 5-year OS of 100%, and 2-year PFS of 75% were observed (Figure 2).

Individual treatment outcomes for patients with EOT-positive disease are listed in *Online Supplementary Table S1*. Of the ten patients with EOT-positive imaging, eight (80%) underwent a biopsy either immediately or after follow-up scanning and all eight were found to have active disease. The remaining two (20%) were not biopsied; they were monitored, and continued to remain in complete response at last follow-up. Biopsies were not performed in these patients because one had active diarrhea at the time of the scan as a possible explanation of new mesenteric lymph node uptake, and the other because of patient-provider preference with repeat scanning showing stability of lymph nodes. All of the eight patients with biopsy-proven disease had residual disease identified on EOT-PET in an initial site of HL involvement. All eight patients with active disease proceeded to salvage therapy, with two (25%) receiving salvage radiotherapy due to localized disease, and six (75%) receiving systemic salvage therapy with autologous stem cell transplant due to more diffuse involvement. After autologous stem cell transplantation, only one patient progressed to needing

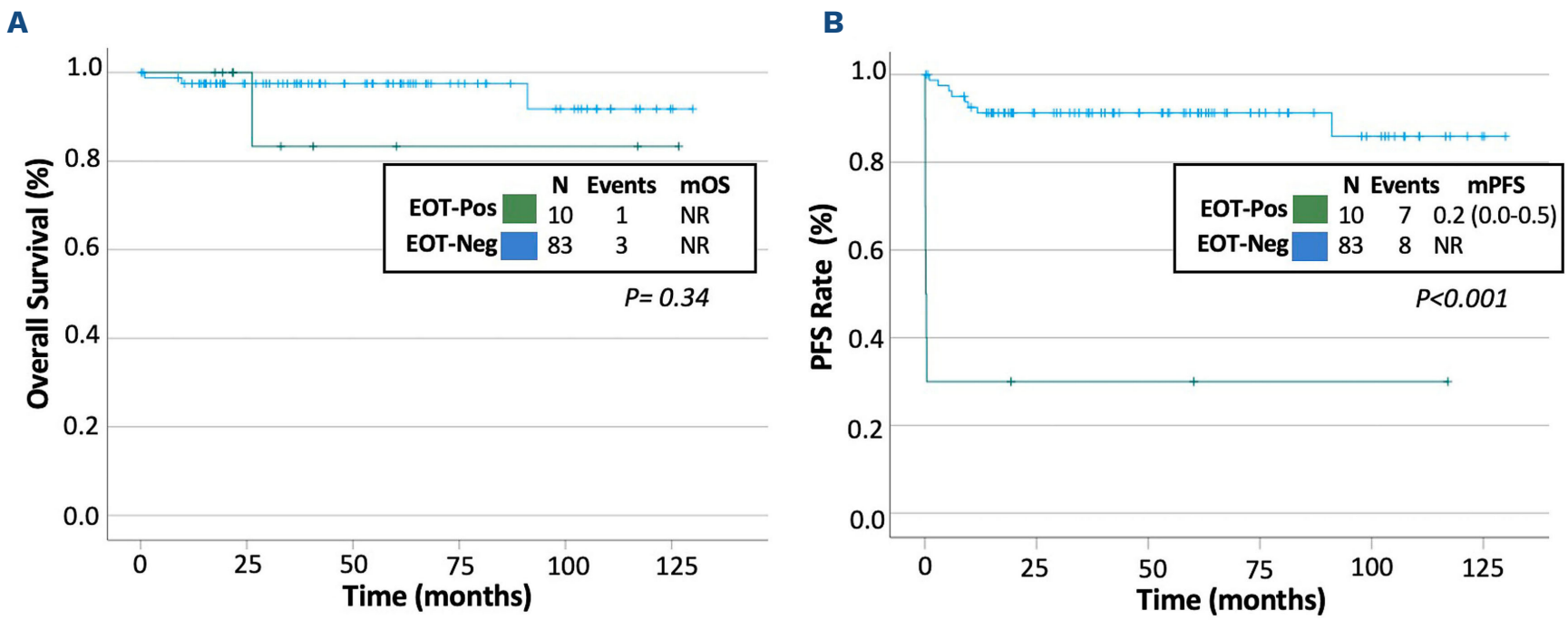

Figure 1. Association of end-of-treatment positron emission tomography findings with overall survival and progression-free survival for the whole cohort. (A) Overall survival. (B) Progression-free survival. N: number of patients; mOS: median overall survival; EOT: end of treatment; pos: positive; neg: negative; PFS progression-free survival; mPFS: median PFS; NR: not reached. The 95% confidence interval is indicated in brackets after the median time.

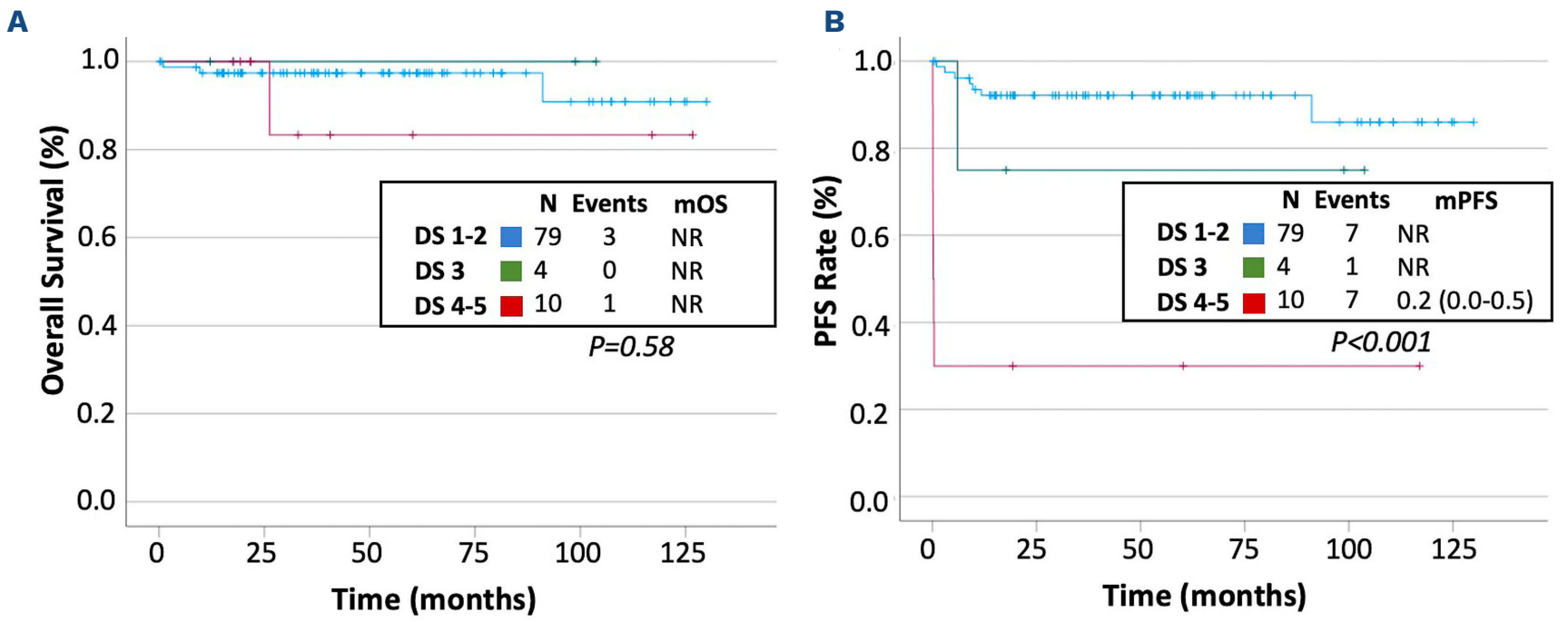

Figure 2. Association of end-of-treatment positron emission tomography findings with overall survival and progression-free survival for the whole cohort and stratified by Deauville score. (A) Overall survival. (B) Progression-free survival. N: number of patients; mOS: median overall survival; DS: Deauville score; PFS progression-free survival; NR: not reached; mPFS: median PFS. The 95% confidence interval is indicated in brackets after the median time.

an allogeneic transplant. At last follow-up, among the eight patients found to have active disease, six patients remained in complete response, one had died due to graft-*versus*-host disease after allogeneic stem cell transplantation, and one continued to undergo treatment.

Most recent trials have not utilized EOT-PET as an endpoint, and observational literature largely predates the standardized evaluation using the DS.[5,6,8,9] In the present study, both interim-positive and EOT-positive PET strongly predicted PFS, with significant associations between both results. Despite the strong prognostic value of the interim scan reported in previous trials and real-world studies, a considerable fraction of patients who were EOT-positive with active disease had an interim-negative scan.[2-4,10] Previously, literature has pointed to EOT-PET having an improved sensitivity over interim-PET due to a potential tumor stunning effect early in treatment, and refractory clones showing initial response but late resurgence during the course of treatment.[8] A previous assessment of 76 patients with HL of all stages found, similarly to our study, that both interim-PET-positive (HR 3.79 [95% CI: 1.37-10.49]) and EOT-PET-positive (≥3) (HR 24.02 [95% CI: 6.59-87.47]) disease were associated with reduced PFS.[11] Certainly, important financial and resource implications need to be considered; how-

ever, our data suggest that in clinical practice, EOT is useful. Suspicion of progression should remain high for those who are EOT-positive regardless of interim-PET results.

Non-specific findings are frequently found on PET scanning, and there are a host of other benign etiologies that can appear like active lymphoma.[7,12] Similar to the findings in our study, a systematic review and meta-analysis found a false-positive rate of 23.1% (95% CI: 4.7%-64.5%) for EOT-PET in HL with the majority of these false-positive cases being due to inflammatory changes.[12] In clinical practice, the decision to observe, biopsy, administer radiotherapy or begin salvage therapy can be exceedingly difficult. In our study, we found that most patients with EOT-positive disease ended up requiring a biopsy, even if initially observed. In those found to have progression, most patients were successfully salvaged with either high-dose chemotherapy and autologous stem cell transplantation or salvage radiotherapy due to localized disease in a small number of patients. Certainly, a risk-benefit relationship exists in obtaining a biopsy. Our cohort suggests that a tissue sample should be obtained soon after an EOT-positive scan, unless there is convincing evidence of another ongoing non-malignant process. The strengths of this study include the blinded uniform review of all PET scans, and granularity regarding outcomes and treatment. Limitations include the retrospective methodology and the associated biases of this design. Due to these, we had incomplete data and imaging on patients also followed outside our institution and were unable to determine exactly the underlying reasons for treatment approaches taken for EOT-positive disease. Additionally, even in assessing a 10-year cohort, as most patients with early-stage HL achieve a complete response in the front-line setting, conclusions were drawn using a small number of patients.

In conclusion, despite recent literature demonstrating the significant prognostic and treatment-related implications of the interim-PET scan, EOT-PET still adds value. With confirmatory biopsy and timely treatment initiation, most patients with EOT-positive disease and biopsy-proven progression can be successively salvaged and have a comparable OS outcome to those with EOT-negative findings. Overall, in early-stage HL, EOT-PET is important for identifying patients with relapsed or refractory disease and is necessary even for those with interim-PET-negative responses.

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Contributions

KLC, JRY, and SMA designed this study, analyzed and interpreted the data, and wrote the manuscript. SL, MAM, AR, HWT, BSH, PBJ, INM, and TMH interpreted the data and assisted in writing the manuscript. All authors provided final approval of the manuscript and are accountable for all aspects of the work.

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The data presented in this study are not available for sharing.

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