ARTICLE

End-of-treatment and serial PET imaging in primary mediastinal B-cell lymphoma following dose-adjusted EPOCH-R: a paradigm shift in clinical decision making

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ABSTRACT

Dose-adjusted-EPOCH-R obviates the need for radiotherapy in most patients with primary mediastinal B-cell lymphoma. End-of-treatment PET, however, does not accurately identify patients at risk of treatment failure, thereby confounding clinical decision making. To define the role of PET in primary mediastinal B-cell lymphoma following dose-adjusted-EPOCH-R, we extended enrollment and follow up on our published phase II trial and independent series. Ninety-three patients received dose-adjusted-EPOCH-R without radiotherapy. End-of-treatment PET was performed in 80 patients, of whom 57 received 144 serial scans. One nuclear medicine physician from each institution blindly reviewed all scans from their respective institution. End-of-treatment PET was negative (Deauville 1-3) in 55 (69%) patients with one treatment failure (8-year event-free and overall survival of 96.0% and 97.7%). Among 25 (31%) patients with a positive (Deauville 4-5) end-of-treatment PET, there were 5 (20%) treatment failures (8-year event-free and overall survival of 71.1% and 84.3%). Linear regression analysis of serial scans showed a significant decrease in SUV_{max} in positive end-of-treatment PET non-progressors compared to an increase in treatment failures. Among 6 treatment failures, the median end-of-treatment SUV_{max} was 15.4 (range, 1.9-21.3), and 4 achieved long-term remission with salvage therapy. Virtually all patients with a negative end-of-treatment PET following dose-adjusted-EPOCH-R achieved durable remissions and should not receive radiotherapy. Among patients with a positive end-of-treatment PET, only 5/25 (20%) had treatment-failure. Serial PET imaging distinguished end-of-treatment PET positive patients without treatment failure, thereby reducing unnecessary radiotherapy by 80%, and should be considered in all patients with an initial positive PET following dose-adjusted-EPOCH-R (*clinicaltrials.gov identifier 00001337*).

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of diffuse large B-cell lymphoma that is clinically and biologically related to nodular sclerosis Hodgkin lymphoma (nsHL).[1,2] As such, it primarily presents as a bulky mediastinal mass in adolescents and young adults and is more common in females.[3-8] R-CHOP is com-

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monly used to treat PMBCL but retrospective studies indicate that this therapy alone is inadequate for many patients,[9] resulting in the frequent use of consolidative mediastinal radiotherapy, as part of combined modality treatment.[6,8,10] It is well documented, however, that mediastinal radiotherapy is associated with significant late toxicity including premature death due to cardiovascular complications and second malignancies,[11-14] which has led to efforts to minimize its use in mediastinal lymphomas.[15-18] In an effort to reduce mediastinal radiotherapy in PMBCL, we conducted a prospective study of DA-EPOCH-R based on hypothesis-generating evidence that dose-intensive regimens may be more effective and showed DA-EPOCH-R obviated the need for radiotherapy in most patients.[4]

An important, albeit preliminary observation from this study, was that most patients with a positive end-of-treatment (EOT) ^{18}F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) scan achieved durable remissions without further therapy, calling into question the positive predictive value (PPV) of EOT FDG-PET following DA-EPOCH-R.[4] This is in line with several other retrospective studies as well as the prospective IELSG-26 study that have eluded to the low PPV and high false-positive rate of EOT FDG-PET imaging in PMBCL; however, a variety of induction chemoimmunotherapy regimens were utilized with most EOT FDG-PET positive patients going on to receive salvage radiotherapy or high-dose chemotherapy with autologous stem-cell transplantation, making the results inapplicable to DA-EPOCH-R or chemotherapy alone.[19-22] While it is routine clinical practice to consider a positive (Deauville 4-5) EOT FDG-PET scan indicative of persistent disease and the need for radiotherapy,[23,24] our findings raise a potential paradigm shift whereby singular EOT FDG-PET scans are inadequate following DA-EPOCH-R. Indeed, even the significance of a negative EOT FDG-PET following front-line chemoimmunotherapy remains an open question and the subject of a randomized phase III study of post-treatment radiotherapy *versus* observation (*clinicaltrials.gov identifier 01599559*).

To fully characterize the role of EOT and serial FDG-PET imaging on clinical decision making and to provide further data on the clinical outcome of DA-EPOCH-R in PMBCL, we significantly extended enrollment on our phase II trial and independent clinical series. Herein, we provide an in-depth analysis of single EOT and serial FDG-PET scans and long-term patient outcome following DA-EPOCH-R for previously untreated PMBCL.

Methods

Patients/Treatment

Ninety-three PMBCL patients received DA-EPOCH-R on the prospective NCI (N=59) and retrospective Stanford (N=34) study from November 1999 through July 2016. This includes 67 patients from the previously published study[4] plus an additional 26 patients; 8 NCI and 18 Stanford. All patients received 6-8 cycles of DA-EPOCH-R (dose-adjusted etoposide, cyclophosphamide, and doxorubicin with prednisone, vincristine and rituximab) with G-CSF support as previously described, without consolidation radiotherapy.[4,25] The study was approved by the NCI IRB and all patients provided written informed consent in accordance with the Declaration of Helsinki. *clinicaltrials.gov identifier 00001337*.

Response Assessment

EOT response assessment was performed using CT in all patients and FDG-PET beginning in September 2002. Published guidelines recommend EOT FDG-PET a minimum of 3 weeks, preferably 6-8 weeks, following completion of chemotherapy.[24] All patients with an EOT FDG-PET following the last dose of chemotherapy up to 8 weeks post-therapy (11 weeks post day 1 of the final cycle) were included for analysis. EOT FDG-PET was performed a median 3 weeks (range, 1-10) from day 1 of the final cycle of therapy. Scans were retrospectively scored per the 5-point Deauville scale[26] with scores 1-3 negative and 4-5 positive.[23,24] Thirty-five of 55 (64%) and 22 of 25 (88%) patients with negative and positive EOT scans, respectively, underwent serial FDG-PET imaging. Tumor biopsy and salvage therapy was implemented per investigator discretion. Surveillance CT scans were performed for up to 5 years post-therapy. One nuclear medicine physician from each institution reviewed and scored all FDG-PET scans from their respective institution without knowledge of clinical outcome. Calculation of metabolic tumor volume (MTV) and total lesion glycolysis (TLG = MTV x SUV_{mean}) was performed on all NCI FDG-PET scans using Osirix version 8.50 (Pixmeo SARL, Bernex, Switzerland).

Statistical Analysis

Overall survival (OS) and event-free survival (EFS) was calculated from the on-study date until date of death or last follow up or date of death, relapse, progression, second lymphoma treatment, or last follow up, respectively. Treatment failure was defined as relapse, progression, or residual disease following therapy. Probabilities of OS/EFS were calculated using the Kaplan-Meier (KM) method,[27] with the significance of the difference between a pair of KM curves determined via an exact log-rank test. Characteristics were compared between patients with and without evaluable EOT FDG-PET scans and between patients by institution. Dichotomous characteristics, ordered characteristics, and continuous parameters were compared using Fisher's exact test, an exact Cochran-Armitage test, and an exact Wilcoxon rank sum test, respectively. Linear regression was used in patients with serial FDG-PET scans to determine the slope of the change in SUV_{max} over time. Tests of the slopes being 0 within each group, tests of slopes among the 3 groups, and pairwise comparisons between 2 groups at a time were done using a Wilcoxon signed rank test, an exact Kruskal-Wallis test and Wilcoxon rank sum test, respectively. All *P*-values are two-tailed and not adjusted for multiple comparisons. Median potential follow up was calculated from the date of enrollment through April 2018, the date of the most recent data update.

Results

Patient Characteristics

Baseline characteristics of the 93 patients from NCI and Stanford were similar aside from a higher proportion of patients with an ECOG of 2-3 (29% *vs.* 3%, *P*=0.00058) in the Stanford cohort [Table 1]. Thirteen patients did not have evaluable EOT FDG-PET scans. Reasons included; treatment prior to routine FDG-PET use (N=9), FDG-PET performed prior to the last dose of chemotherapy (N=2), FDG-PET performed later than 8 weeks post completion of chemotherapy (N=1), and extensive brown fat uptake (N=1); exclusion of the 3 patients with FDG-PET scans had no significant impact on the study results or conclusions. The 80 remaining patients with evaluable EOT FDG-PET scans had similar baseline characteristics to the

Table 1. Baseline Characteristics of the Study Patients.

Characteristic	Total Cohort (N=93)	Evaluable EOT FDG-PET (N=80)	Prospective NCI Cohort (N=59)	Retrospective Stanford Cohort (N=34)
Female sex- no. (%)	55 (59)	44 (55)	35 (59)	20 (59)
Age- yr.				
Median	31	31	30	32.5
Range	18-68	18-68	19-54	18-68
Bulky tumor, > 10 cm				
Patients- no. (%)	54 (59)[a]	52 (66)[b,d]	36 (61)	18 (55)[c]
Maximal diameter- Median (Range), cm	10.7 (4-18.9)	10.9 (5.5-18.9)[e]	10.9 (4-18.9)	10 (4.9-18.3)
Stage IV disease- no. (%)	18 (19)	14 (18)	14 (24)	4 (12)
International prognostic index (IPI)- no. (%)				
Low (0-1)	60 (65)	53 (66)	37 (63)	23 (68)
Low-intermediate (2)	22 (24)	18 (23)	15 (25)	7 (21)
Intermediate-high (3)	8 (9)	7 (9)	6 (10)	2 (6)
High (4-5)	3 (3)	2 (3)	1 (2)	2 (6)
ECOG- no. (%)				
0-1	81 (87)	69 (86)	57 (97)	24 (71)
2-3	12 (13)	11 (14)	2 (3)[f]	10 (29)
Elevated LDH- no. (%)	68 (74)[a]	59 (75)[b]	46 (78)	22 (65)[c]
Extranodal site- no. (%)				
0-1	80 (86)	69 (86)	50 (85)	30 (88)
≥ 2	13 (14)	11 (14)	9 (15)	4 (12)
Any	38 (41)	30 (38)	27 (46)	11 (32)
Pleural effusion- no. (%)	45 (48)	40 (50)	27 (46)	18 (53)
Pericardial effusion- no. (%)	38 (41)	35 (44)	21 (36)	17 (50)

[a]N = 92 patients; [b]N = 79 patients; [c]N = 33 patients; [d]*P*=0.0013 comparing patients with and without evaluable EOT FDG-PET scans; [e]*P*= 0.0009 comparing patients with and without evaluable EOT FDG-PET scans; [f]*P*=0.00058 comparing patients treated at NCI *vs.* Stanford; ECOG: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; EOT FDG-PE: end-of-treatment; ^{18}F-fluorodeoxyglucose-positron-emission tomography; NCI: National Cancer Institute.

13 patients without evaluable scans other than significantly more bulky tumors > 10 cm (66% *vs.* 15%, *P*=0.0013).

Clinical Outcome

With a median potential follow up of 8.4 years (range, 1.7-18.4), EFS and OS at 8-years is 90.6% (95% confidence interval [CI]; 81.8-95.2) and 94.7% (95% CI; 86.3-98.0), respectively [Figure 1 A-B]. The NCI and Stanford cohorts had similar outcome with an 8-year EFS of 90.6% *vs.* 91.0% (*P*=0.71) and OS of 95.6% *vs.* 93.8% (*P*=0.30), respectively [Figure 1 C-D]. The outcome of the 13 patients without evaluable EOT FDG-PET scans was not statistically different from the 80 patients with evaluable scans; 8-year EFS 100% *vs.* 89.0% (*P*=0.17) and OS 100% *vs.* 93.8% (*P*=0.24), respectively.

EOT FDG-PET and CT Response

Eighty (86%) patients had evaluable EOT FDG-PET scans following DA-EPOCH-R. Fifty-five (69%) patients had a negative (Deauville 1-3) and 25 (31%) patients had a positive (Deauville 4-5) EOT FDG-PET [Table 2]. Treatment failure occurred in 1 of 55 (2%) patients with a negative EOT FDG-PET and in 5 of 25 (20%) patients with a positive EOT FDG-PET scan. All 5 treatment failures in patients with a positive EOT FDG-PET occurred at or immediately following the EOT FDG-PET scan, and the one treatment failure in the patient with a negative EOT FDG-PET occurred at day 320. One of 17 (6%) Deauville 4 patients and 4 of 8 (50%) Deauville 5 patients had treatment failure following front-line therapy. Four of 6 (67%) treatment failures were successfully salvaged with radiotherapy alone in 2 (both Deauville 5), resection alone in 1 (Deauville 4), and chemotherapy/transplantation/radiotherapy in 1 (Deauville 2) with a median remission duration of 6.4 years (range, 2-11.3). Two patients (both Deauville 5) died of progressive disease 7 and 17 months after multiple salvage regimens and 2 patients died without disease.

Patients with a negative (Deauville 1-3) EOT FDG-PET had a significantly better 8-year EFS of 96.0% *vs.* 71.1% (*P*=0.0010) and OS of 97.7% *vs.* 84.3% (*P*=0.0115) compared to patients with positive (Deauville 4-5) scans [Figure 2 A-B]. In an exploratory analysis, patients with Deauville 5 scans had the poorest outcome with an 8-year EFS of 50% *vs.* 93.3% (*P*=0.0003) and OS of 75% *vs.* 95.9% (*P*=0.029) compared to patients with Deauville 1-4 scans [Figure 2 C-D]. Using conventional groupings of Deauville 1-3 *versus* 4-5, EOT FDG-PET had a positive predictive value (PPV) of 20% and a negative predictive value (NPV) of 98%.

All 89 patients with complete tumor measurements had a reduction in the bi-dimensional product of the largest tumor mass by CT. There was no relationship between EOT tumor reduction and EOT FDG-PET Deauville score

[Figure 3]. Furthermore, there was no difference in tumor reduction when comparing patients with (N=6) and without (N=83) treatment failure; median reduction of 92% (range, 65-99) *vs.* 93% (range, 62-100), respectively [Figure 3].

Serial FDG-PET Scans

Fifty-seven of 80 patients with evaluable EOT FDG-PET scans underwent 144 total serial scans; median of 2 (range, 1-6). Among the 54 patients with a negative EOT FDG-PET who are progression-free, 34 had serial scans. Linear regression analysis demonstrated an overall decrease in SUVmax over time with a median change per day in SUV_{max} of -0.005 (range, -0.134-0.010; *P*=0.0018) [*Online Supplementary Figure S1A*]. Among the 20 patients with a positive EOT FDG-PET who are progression-free, 17 had serial scans. SUV_{max} decreased in these patients as well with linear regression analysis revealing a median change per day in SUV_{max} of -0.006 (range, -0.070-0.002; *P*=0.0005) [Figure 4A].

In the 6 treatment failures, the median EOT FDG-PET SUV_{max} was 15.4 (range, 1.9-21.3) [Figure 4C]. All 6 treatment failures had evidence of disease, which was documented by biopsy in 4 and by standard imaging criteria in 2 patients. One patient without biopsy confirmation showed progression on CT with an EOT SUV_{max} of 14.5 and received salvage radiotherapy. A second patient without biopsy showed progression on treatment with increases in SUV_{max} from 10.2 to 21.3, and appearance of a new lesion, and received radiotherapy. Serial scans in 5 treatment failures all revealed progressive increases in SUV_{max}, which normalized in 3 patients following radiotherapy, resection, and chemotherapy/transplantation/radiotherapy, respectively. Two patients had continued progression of SUVmax despite multiple salvage therapies and both died of progressive disease. Linear regression analysis in the 5 treatment failures with serial scans showed an overall increase in SUVmax per day across serial scans, with a median of 0.023 (range, -0.007-0.267; *P*=0.13), which was statistically greater than both positive and negative EOT FDG-PET non-progressors (*P*=0.011 and *P*=0.0037, respectively).

Among 51 non-progressing patients with serial scans, 10 (20%) continued to have positive and 29 (57%) continued to have negative Deauville scores. Seven (14%) patients converted from positive to negative and 5 (10%) converted from negative to positive [Figure 4B; *Online Supplementary Figure S1B*]. In the 5 patients with treatment failure and serial scans, Deauville score remained stable in 4 (80%) and increased in 1 (20%) [Figure 4D].

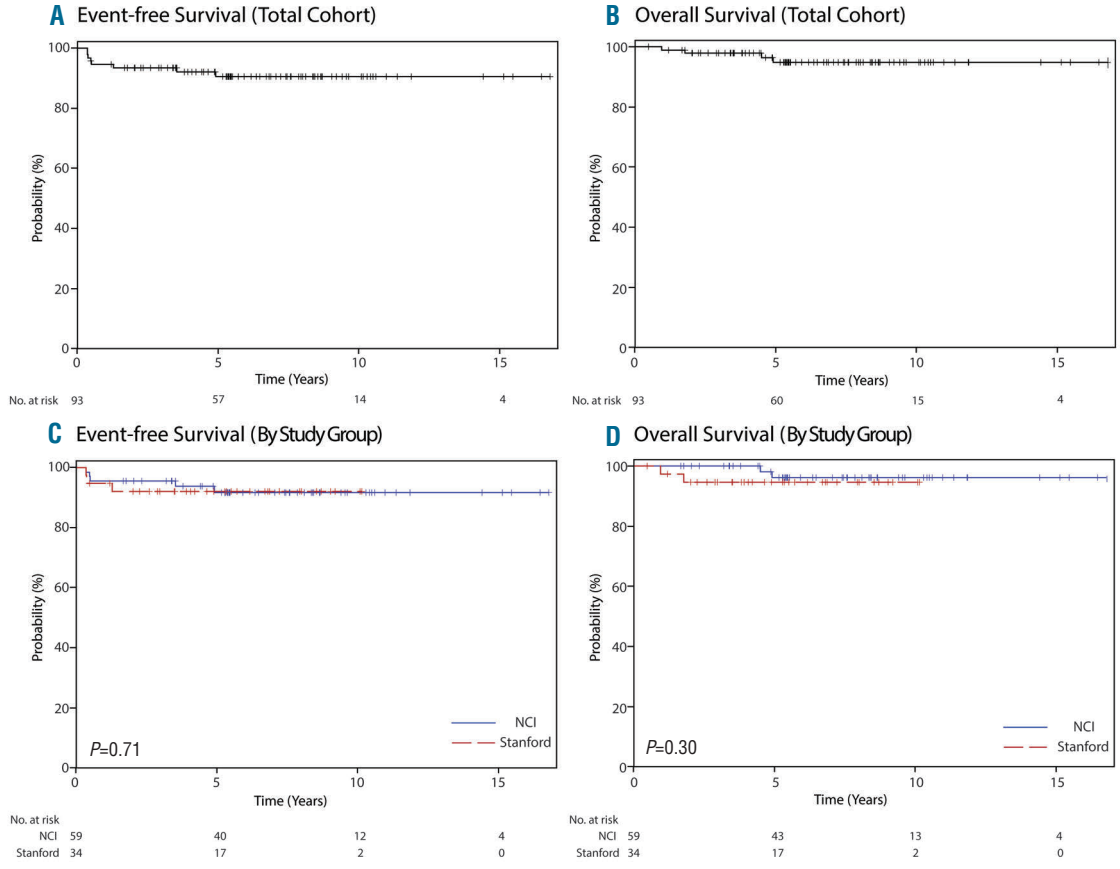

Figure 1. Kaplan–Meier estimates of event-free and overall survival of all patients and by study group. DA-EPOCH-R was administered to a total of 93 patients; 59 treated on the NCI prospective study and 34 treated on the retrospective Stanford study. (A). Event-free survival 90.6% (95% CI, 81.8-95.2) at 8-years for the total cohort. (B). Overall survival 94.7% (95% CI, 86.3-98.0) at 8-years for the total cohort. (C). Event-free survival 90.6% (95% CI, 78.8-96.0) for the NCI cohort and 91.0% (95% CI, 74.6-97.0) for the Stanford cohort (*P*=0.71) at 8-years. (D). Overall survival 95.6% (95% CI, 83.5-98.8) for the NCI cohort and 93.8% (95% CI, 77.5-98.4) for the Stanford cohort (*P*=0.30) at 8-years.

Changes in MTV and TLG across serial FDG-PET scans generally mimicked that of SUV_{max} with greater variability in value between patients within each EOT FDG-PET subgroup [*Online Supplementary Figures S2-3*].

Discussion

These extended results from our initial study[4] show that DA-EPOCH-R in untreated PMBCL patients results in an 8-year EFS and OS of 90.6% and 94.7%, respectively, while obviating the need for radiotherapy in all but 5 (5%) patients. In contrast, retrospective studies suggest R-CHOP alone is inadequate for many PMBCL patients due to an unacceptable rate of primary induction failure up to 21% in one series,[9] necessitating the frequent use of post-treatment radiotherapy, as part of combined modality treatment.[5-10,15,19,21] A recent multicenter, retrospective study comparing R-CHOP to DA-EPOCH-R as front-line therapy for PMBCL showed no significant difference in 2-year PFS or OS between the two treatments; however, this was achieved through significantly greater radiotherapy use with R-CHOP (59% *vs.* 13%, $P<0.001$).[28] Although excellent outcomes can be achieved via combined modality treatment, routine mediastinal radiotherapy use significantly increases the risk of late toxicity, including premature death from cardiovascular disease and second cancers.[11-14] Unfortunately, due to the absence of prospective studies of R-CHOP in PMBCL, an accurate assessment cannot be made of its curative potential and who requires post-treatment radiotherapy. Nonetheless, it is presently accepted that patients with a positive EOT FDG-PET scan following R-CHOP require consolidation radiotherapy, and it remains uncertain if patients with a negative EOT FDG-PET benefit from radiotherapy, which is the endpoint of the IELSG-37 phase III randomized study (*clinicaltrials.gov identifier 01599559*).

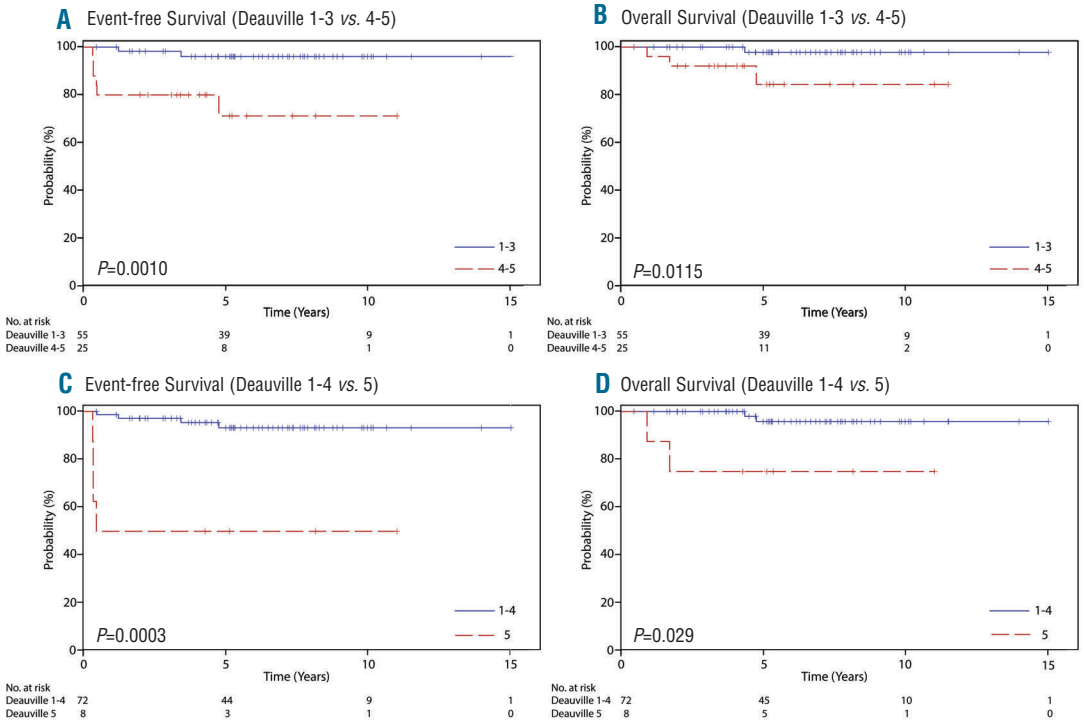

Figure 2. Kaplan–Meier estimates of event-free and overall survival by Deauville group. Event-free survival and overall survival according to EOT FDG-PET Deauville group. (A). Event-free survival 96.0% (95% CI, 84.8-99.0) *vs.* 71.1% (95% CI, 43.6-86.9) (P=0.0010) for Deauville 1-3 (blue curve) and Deauville 4-5 (red curve), respectively, at 8-years. (B). Overall survival 97.7% (95% CI, 84.6-99.7) *vs.* 84.3% (95% CI, 56.5-95.0) (P=0.0115) for Deauville 1-3 (blue curve) and Deauville 4-5 (red curve), respectively, at 8-years. (C). Event-free survival 93.3% (95% CI, 82.8-97.5) *vs.* 50.0% (95% CI, 15.2-77.5) (P=0.0003) for Deauville 1-4 (blue curve) and Deauville 5 (red curve), respectively, at 8-years. (D). Overall survival 95.9% (95% CI, 84.5-99.0) *vs.* 75.0% (95% CI, 31.5-93.1) (P=0.029) for Deauville 1-4 (blue curve) and Deauville 5 (red curve), respectively, at 8-years.

Table 2. EOT FDG-PET Response Following DA-EPOCH-R Therapy.

Lymphoma Status (N=80 total with EOT FDG-PET)	Deauville Score				
	Negative (55/80, 69%)			Positive (25/80, 31%)	
	1	2	3	4	5
	(30%)	(24%)	(15%)	(21%)	(10%)
No treatment failure- no. patients	24*	18	12	16*	4
Treatment failure- no. patients	0	1	0	1	4

*Indicates 1 patient death without evidence of disease recurrence; EOT FDG-PET end-of-treatment 18F-fluorodeoxyglucose-positron-emission tomography.

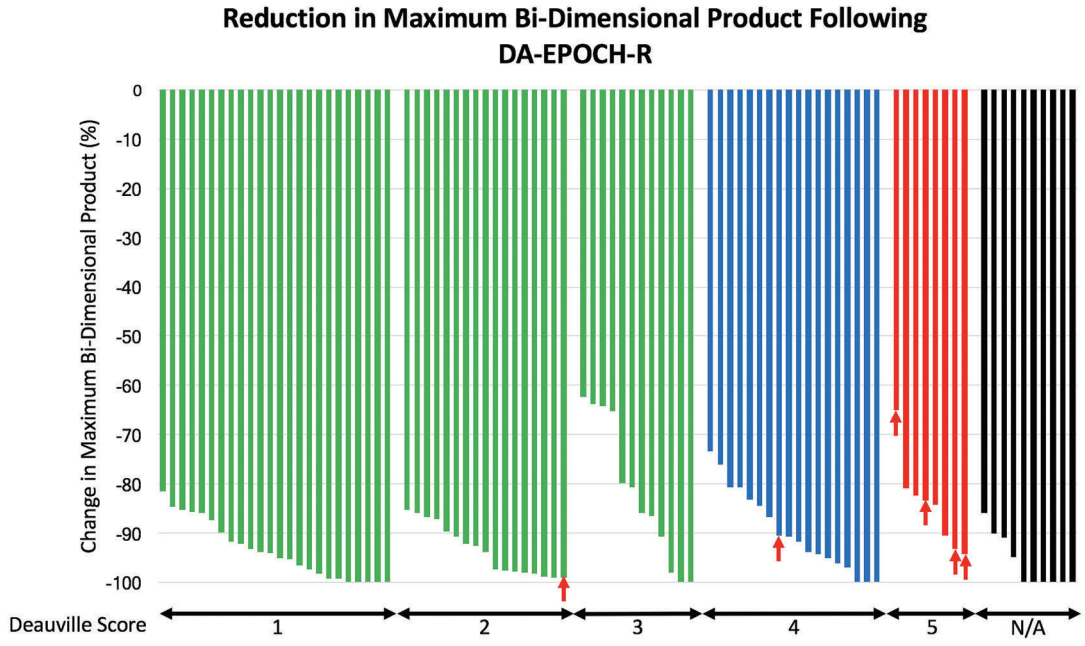

Figure 3. Tumor reduction by end-of-treatment CT. Reduction of the bi-dimensional product of the largest mediastinal mass for the 89 patients with complete tumor measurements by EOT CT. All patients had reduction in tumor bi-dimensional product and there was no relationship between EOT tumor reduction and EOT FDG-PET Deauville score. No difference in tumor reduction was demonstrated between patients with (N=6, red arrows) and without (N=83) treatment failure; Median reduction 92% (range, 65-99) *vs.* 93% (range, 62-100), respectively.

Our results indicate that very few patients require post-treatment radiotherapy following DA-EPOCH-R, irrespective of their EOT FDG-PET scans. These findings provide substantial evidence that patients with negative EOT FDG-PET scans rarely recur and are unlikely to benefit from additional mediastinal radiotherapy. Furthermore, they provide evidence for our initial observation that most patients with a positive EOT FDG-PET achieve long-term remission following DA-EPOCH-R and, as a group, would not benefit from empirical consolidation radiotherapy. Indeed, the discrepancy between our findings that routine consolidation radiotherapy is unnecessary following DA-EPOCH-R, and the accepted need for post-treatment radiotherapy in patients with positive EOT FDG-PET scans following R-CHOP has led to uncertainty. Unfortunately, it is not uncommon for patients with a positive EOT FDG-PET following DA-EPOCH-R to receive post-treatment radiotherapy. Such an approach in our study would have resulted in 31% (25/80) of patients receiving radiotherapy, most of whom (80%) were already cured with DA-EPOCH-R alone.

A clinically important aspect of our study is distinguishing treatment failures following DA-EPOCH-R. Given the worse outcome of PMBCL compared to DLBCL with salvage therapy,[29] early recognition of patients with persistent disease is critical to optimize the curative potential of radiotherapy while averting its use in patients already cured with DA-EPOCH-R. We first looked at tumor mass reduction based on EOT CT, and observed no predictive value on outcome or any relationship with EOT FDG-PET. We also assessed the ability of single EOT and serial FDG-PET imaging to detect treatment failure. Following DA-EPOCH-R, 69% of patients had a negative EOT FDG-PET. Notably, 98% of these patients never progressed, indicating such patients rarely require radiotherapy. Among the 31% of patients with positive EOT scans, only 5 ultimately had treatment failure of which 4 occurred in patients with Deauville 5 scans. These results are consistent with the prospective IELSG-26 study, which revealed a significantly worse outcome in patients with Deauville 4-5 EOT FDG-PET scans (5-yr. PFS 68% *vs.* 99%, $P<0.0001$; 5-yr. OS 83% *vs.* 100%, $P=0.003$), with the greatest number of treatment failures in Deauville 5 patients.[22] In contrast to our study, however, variable chemoimmunotherapy was used and most patients (89%) received consolidation radiotherapy.

We found serial FDG-PET imaging to be a highly effective strategy to distinguish persistent disease from post-treatment inflammatory changes. Linear regression analysis in 17 non-progressing patients with a positive EOT FDG-PET and serial imaging showed an overall decrease in SUV_{max} across serial scans. In contrast, serial FDG-PET imaging in 5 treatment failures with serial scans showed an increase in SUV_{max} that was statistically greater than patients who never progressed, regardless of EOT FDG-PET response ($P=0.011$ and $P=0.0037$ for positive and negative EOT FDG-PET non-progressors, respectively). Overall, use of serial FDG-PET imaging effectively reduced radiotherapy from a potential 31% (25/80) of patients with a positive EOT FDG-PET scan to only 5 (5%) patients with confirmed treatment failure.

We also explored the use of quantitative FDG-PET parameters (i.e., MTV and TLG) to assess if they improved upon SUV_{max} in identification of treatment failures. These methods were limited by the overall low volume of disease following therapy as well as inability to exclude non-malignant causes of FDG uptake, resulting in a wide variability in value between patients. Although these param-

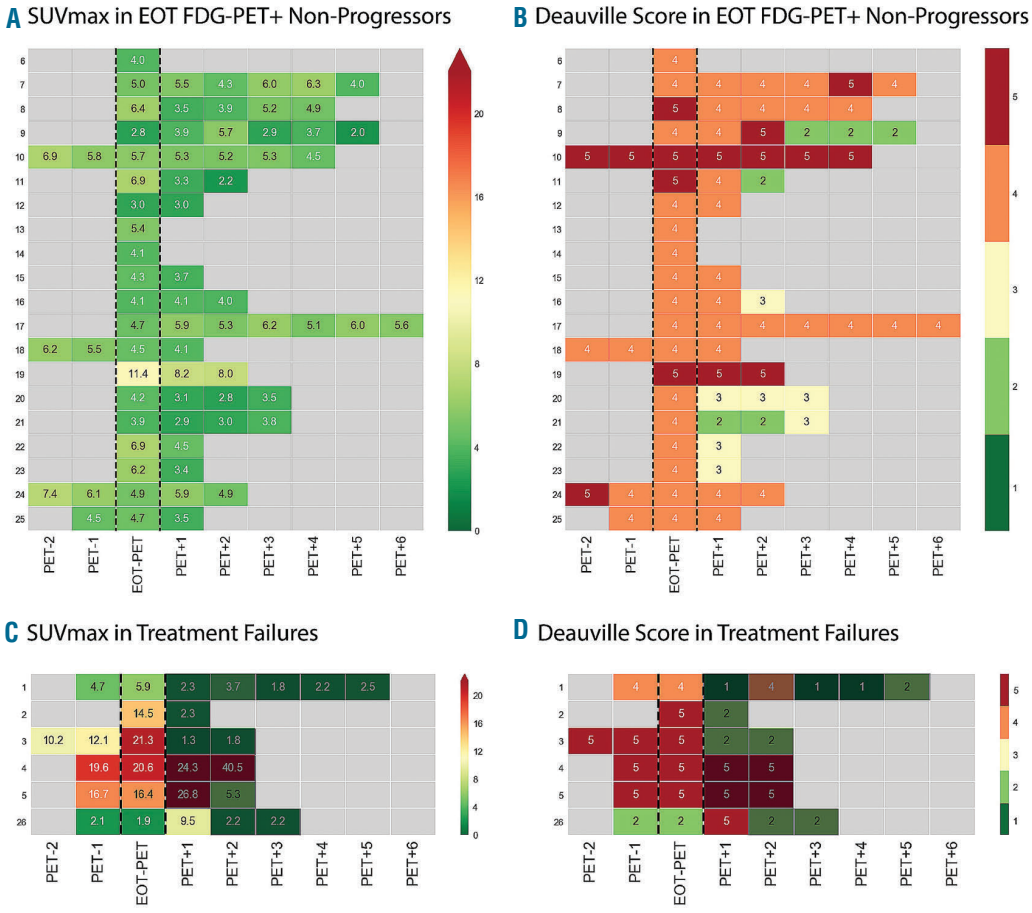

Figure 4. Evolution of serial FDG-PET imaging. Heatmap depiction of (A). SUV_{max}, and (B). Deauville score, over time in the 20 non-progressing patients with a positive EOT FDG-PET scan. Heatmap depiction of (C). SUV_{max}, and (D). Deauville score, over time in the 6 patients with treatment failure. FDG-PET scans performed prior to the EOT FDG-PET are listed as negative numbers with those following the EOT FDG-PET listed as positive numbers. The EOT FDG-PET scan is bordered by black dashed lines. FDG-PET scans performed following salvage intervention are shaded in black.

eters were not superior to monitoring SUV_{max} in our study, other recent reports indicate these quantitative parameters may be beneficial for baseline prognostication as well as when combined with EOT Deauville score.[30,31]

Our findings are supported by a recent retrospective multi-center analysis of 156 PMBCL patients treated with DA-EPOCH-R which reported a 3-year EFS and OS of 85.9% and 95.4%, respectively.[32] Overall, 14.9% of patients received post-treatment radiotherapy, which was administered at the discretion of the treating physician. In that study, 75% of patients achieved a negative EOT FDG-PET and 95.4% remained progression-free, consistent with our findings that consolidation radiotherapy is virtually never indicated in this patient group. Less clear are their results in patients with positive EOT FDG-PET scans. Among the 31 patients with positive EOT scans, 19 received no further treatment with 68% progression-free at a median follow up of 17 months, indicating that a substantial subset of these patients are likely cured with DA-EPOCH-R alone.[32] Twelve patients with a positive EOT FDG-PET received post-treatment radiotherapy and 33.3% remain progression-free at 2 years.

It is important to note that serial FDG-PET was not a prospective endpoint of our trial and decisions regarding which patients should receive serial scans and the timing of those scans was left to the discretion of the treating physician. Indeed, the aim of this study was to provide a descriptive look at EOT and serial PET imaging in PMBCL following DA-EPOCH-R as it occurs in the real-world clinical setting, where decisions are often left to clinical judgement. The notion, however, that physician discretion influenced these observational findings is obviated by the extended follow up, which showed who did and did not recur and by the absence of late recurrences.

In conclusion, our results indicate that a negative EOT FDG-PET following DA-EPOCH-R in PMBCL is highly predictive of cure and radiotherapy in these patients is unnecessary. The unique biology of PMBCL results in a high rate of false-positive EOT FDG-PET scans indicating the need for a paradigm shift in clinical decision making for this group of patients when receiving DA-EPOCH-R. A singular EOT FDG-PET did not accurately identify treatment failure but serial FDG-PET imaging effectively discriminated residual disease from post-treatment inflammatory changes. Serial FDG-PET imaging should be considered in all patients with an initial positive EOT FDG-PET to identify treatment failures that require radiotherapy.

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