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Letter
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PET for Response Assessment to R-da-EPOCH in Primary Mediastinal Large B-cell lymphoma: Who Is Worthy to be Irradiated?

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Anthracycline-based chemoimmunotherapy (CIT) has improved the outcomes in primary mediastinal large B-cell lymphoma (PMLBCL).[1–3] Current research focuses on minimizing radiotherapy (RT) use by positron emission tomography/computed tomography (PET/CT)-adapted decisions, intensification of CIT, or both.[4–7] The National Cancer Institute (NCI) introduced the intensified rituximab and dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin (R-da-EPOCH) regimen, which produced better results than historically achieved with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), while minimizing consolidative RT.[7–9]

At the end-of-treatment (EoT), residual masses are very common. Positron emission tomography/computed tomography (PET/CT) is required to address their clinical significance. Following R-CHOP, even patients with Deauville 5-point scale score (D5PSS) 3 achieve >90% long-term disease control without consolidative RT.[6] Consolidative RT produces 80%–87% long-term disease control rate in D5PSS-4 patients following R-CHOP or rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (R-MACOP-B), but patients with D5PSS-5 experience inferior outcomes.[4–6,10,11] Following R-da-EPOCH, it is advised to avoid RT not only in EoT-PET-negative patients but also in those with D5PSS-4/5, as serial PET/CT imaging typically shows stability or regression

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without further intervention.[7,8] As these conclusions are based on limited data of 80 patients, optimal handling of patients with D5PSS-4/5 following R-da-EPOCH has not been adequately studied yet. We provide here an extensive real-world experience on EoT-PET imaging after R-da-EPOCH, aiming to assess its clinical significance and effect on treatment guidance.

Patients were eligible for inclusion if they met previously described criteria to define PMLBCL[1,4,5,12] and had received R-da-EPOCH in a multicenter setting across Greece (n = 145; 2014–2022). EoT-PET/CT-scan was performed in 139 of 145 patients; in 2 of 139 PET was negative after 3–4 cycles and was not repeated at EoT. Two additional patients with clearly progressive disease (PD) by conventional staging did not undergo PET/CT and were considered as D5PSS-5. Among the remaining 4 patients, 1 died during the first cycle of gastrointestinal hemorrhage, and 3 have not yet undergone EoT-PET due to COVID-19 infection, technical issues and loss to follow-up.

Delivery of R-da-EPOCH was planned as per the original treatment protocol, but protocol deviations in the real-life were recorded.[7,13] In responding patients per Cheson 1999 criteria,[14] RT was used at the discretion of the treating physician. Following a commonly established policy, RT was omitted in the overwhelming majority of patients with negative PET/CT (D5PSS-1/2/3) and in most patients with D5PSS-4 per local interpretation.[15] Due to its crucial significance, central retrospective review was performed in 20 of 22 cases with D5PSS-4 by visual assessment. The ratio of maximum standardized uptake value (SUV_{max}) of the lesion and the liver ($SUV_{maxles}/SUV_{maxliv}$) was calculated and evaluated at the cutoff of 1.4 (criterion 1.4x).[16] Freedom from progression (FFP) and overall survival (OS) were defined as previously reported.[4,5]

The baseline characteristics of the 145 eligible patients are shown in Suppl. Table S1. The protocol was strictly followed in 81 of 131 patients (62%) with available data. With a median follow-up of 29.8 months (range, 1.3–94.9; interquartile range [IQR], 17.5–51.8) for the 123 patients without progression (n = 18) or salvage autologous stem cell transplantation ([ASCT]; n = 4), the 5-year FFP and OS, measured from treatment initiation, were 86.6% and 92.7% with all 9 deaths being disease related.

According to the Deauville criteria, 24 of 141 evaluable patients (17%) had D5PSS-1, 35 (25%) D5PSS-2, 42 (30%) D5PSS-3, 22 (16%) D5PSS-4, and 17 (12%) D5PSS-5. A single patient (0.7%) had D5PSS-X (indeterminate) and was classified as negative, as he had a new small splenic lesion (SUV_{max} = 5.9) with no baseline splenic disease and remission in all other disease sites (resolved later, remains in complete remission [CR]). Among patients with D5PSS-4, only 3 of 22 had $SUV_{max} \geq 5$. All patients with D5PSS-5 had $SUV_{max} \geq 5$, and 87% $SUV_{max} \geq 10$ (range, 7.7–27.7).

Among the 130 patients with conventionally responding disease, the frequency of D5PSS-1, 2, 3, X, 4, and 5 was 19%, 27%, 32%, 0.8%, 17%, and 5%, respectively. The baseline characteristics—including protocol adherence—did not differ between patients with EoT-PETD5PSS 1-3/X, 4, and 5, as shown in Suppl. Table S1. The 5-year FFP rates for patients with D5PSS-1, 2, 3, 4, and 5 were 95.7%, 97.1%, 97.5%, 86.4%, and 29.4% ($P < 0.001$; Figure 1A). The 5-year OS rates for patients with D5PSS-1-4/X versus 5 were 99.1% versus 56.7% ($P < 0.001$; Figure 1B).

Among EoT-PET-negative patients, only 3 of 102 (3%) received consolidative RT: 0 of 24, 1 of 35 (3%), and 2 of 42 (5%) with D5PSS-1, 2, 3, respectively. Relapses were observed in 3 of 102 (3%); one with D5PSS-1, D5PSS-2, and D5PSS-3 each for a 5-year FFP of ≈97.0% (95.7%, 97.1%, and 97.5% for D5PSS-1, 2, 3, respectively [$P = 0.92$; Figure 1A]). Only the patient with D5PSS-1 had systemic, disseminated relapse. The 2 patients with D5PSS-2/3 had a central nervous system (CNS) component. In EoT-PET-negative patients, 4 additional events of special clinical interest were observed: one D5PSS-1 patient developed classical Hodgkin lymphoma (cHL) 14 months from R-da-EPOCH initiation and 3 D5PSS-3 patients developed therapy-related acute myeloid leukemia (t-AML) at 10, 22, and 24 months. All 4 are currently alive.

Among 22 of 141 (16%) patients with D5PSS-4 per local interpretation, only 5 of 22 received RT. Only 3 of 22 relapsed—all non-irradiated—for a 5-year FFP of 86.4% (Figure 1A), which was 100% versus 82.4% for irradiated versus non-irradiated patients ($P = 0.33$; Figure 1C). In 20 of 22 patients with D5PSS-4 per local interpretation, EoT-PET were available for central review. By visual interpretation, 7 of 20 cases (35%) were reclassified as D5PSS-3 ($SUV_{maxles}/SUV_{maxliv}$ 1.03–2.58). At the cutoff of 1.4x, $SUV_{maxles}/SUV_{maxliv}$ was discriminative between revised D5PSS-3 and D5PSS-4. The median $SUV_{maxles}/SUV_{maxliv}$ for patients reclassified as D5PSS-3 was 1.15 (range, 1.03–1.36; all ratios <1.4x) versus 1.72 (range, 1.31–2.58; 11/13 ratios >1.4x) for those reclassified as D5PSS-4. The 2 patients without EoT-PET available for review had $SUV_{maxles}/SUV_{maxliv}$ ratios 2.73 and 1.44. As they fulfilled the criterion 1.4x, they were reclassified as revised D5PSS-4. Following central review, 2 of 3 relapses were observed in patients with revised D5PSS-4, but the third was observed in a patient reclassified as D5PSS-3. The latter relapse was very slow, was not histologically confirmed, salvaged with RT and followed by further relapse as cHL, 31 months later. According to the revised data, 3 of 49 (6%) patients with D5PSS-3 received RT and 2 of 49 relapsed for a 5-year FFP of 95.5% (Figure 1D). Only 4 of 15 (27%) patients with revised D5PSS-4 received RT. Only 2 of 15 relapsed—both non-irradiated—for a 5-year FFP of 86.7% (Figure 1D), which was 100% versus 81.8% for irradiated versus non-irradiated patients ($P = 0.38$; Figure 1E).

Among 17 patients with D5PSS-5, six had responsive disease by conventional staging and 11 had stable disease (SD) or PD. The median SUV_{max} in responding patients (partial remission [PR]) compared to SD/PD was 11.05 (range, 7.7–15.0) versus 21.8 (12.8–27.7) ($P = 0.002$) with minimal overlap (Table 1). Among conventional responders, 5 of 6 received RT and all converted to PET-negative and remain in CR. The responder with the highest SUV_{max} = 15.0 was directly forwarded to salvage chemotherapy and died. All 11 patients with SD/PD were directly forwarded to salvage chemotherapy/ASCT: 5 of 11 have died, 2 of 11 are receiving second-line salvage therapy, and 4 of 11 are in CR. The 5-year OS was 83.3% versus 40.9% for patients with responsive D5PSS-5 versus resistant D5PSS-5 ($P = 0.13$; Figure 1F).

The present study not only validates previous data but also highlights novel aspects of R-da-EPOCH treatment in PMLBCL, including the role of RT in a highly selected minority of EoT-PET-positive cases, the variability of D5PSS-4 interpretation in real-life, the importance of combining EoT-PET with CT-based data, and the worrisome occurrence of t-AML in very few—but otherwise cured—patients.

The relapse rate among EoT-PET-negative patients after R-da-EPOCH was minimal and the 3 relapses would not have been prevented with mediastinal RT, since two of them were localized to the CNS, similarly to observations after R-CHOP[4,5,17,18], and the third was an early, widely disseminated relapse. Only the patient relapsed as cHL, a well-established either early or delayed event,[19] might benefit by additional RT. Thus, RT in EoT-PET-negative patients after R-da-EPOCH is clearly clinically irrelevant with a number need-to-treat of 51. These findings are in line with the recent International Extranodal Lymphoma Study Group (IELSG)-37 study,[20] validate the original R-da-EPOCH dataset,[7] and suggest that the omission of RT remains valid even if the strict escalation process is violated in a sizeable minority of them, as often seen in real-life.[13]

Patients with D5PSS-4 EoT-PET were not irradiated in the combined NCI/Stanford series with only 1 of 17 progressing and successfully salvaged with resection alone.[7,8] Although inferior outcomes have been reported by others despite RT,[9,21]

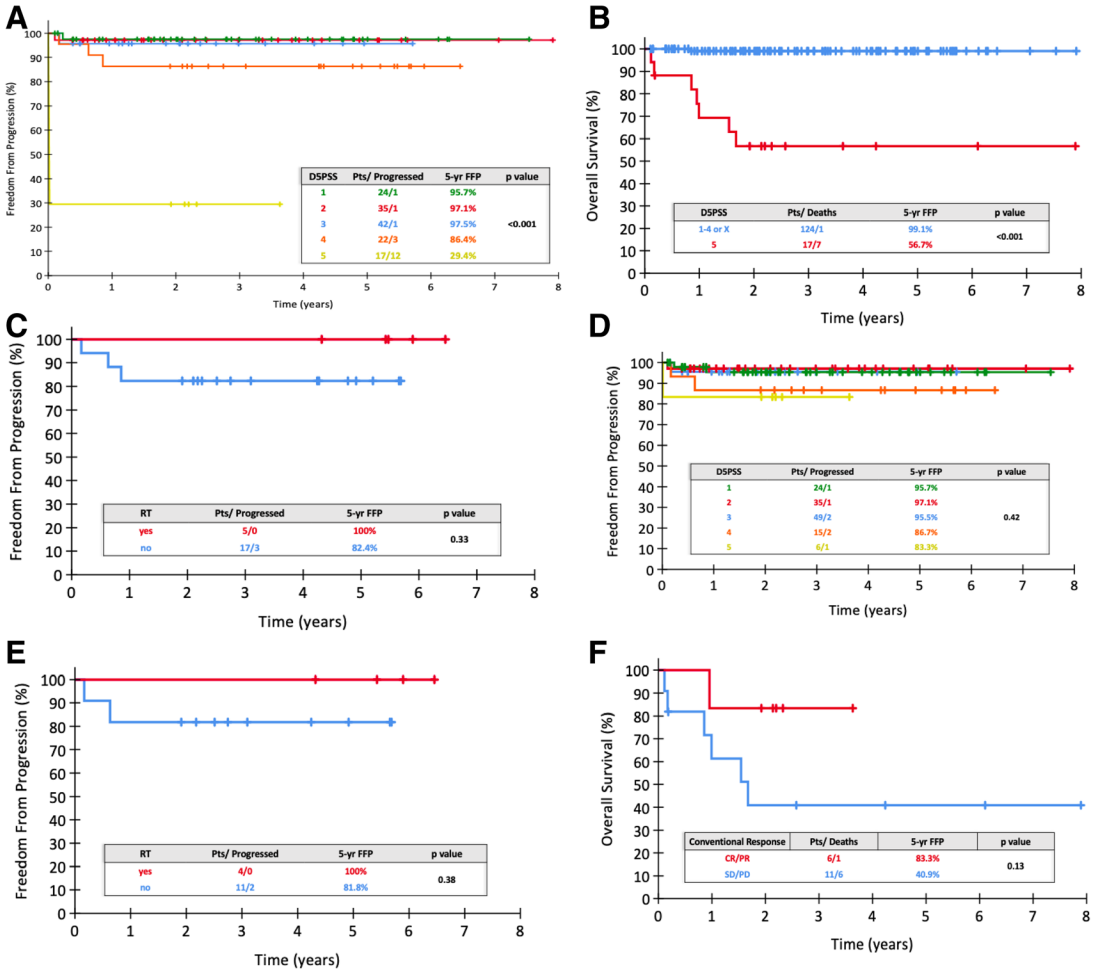

Figure 1. Survival outcomes by EoT-PET status after R-da-EPOCH. (A) Freedom from progression rates by Deauville 5-point scale classification. (B) Overall survival by Deauville 5-point scale classification (1, 2, 3, or X collectively vs 5). (C) Freedom from progression by the use of consolidative radiotherapy in patients with D5PSS 4 per local interpretation. (D) Freedom from progression among patients with conventionally responding disease by Deauville 5-point scale classification after central review of 20 patients with Deauville 5-point scale score 4 per local interpretation. (E) Freedom from progression by the use of consolidative radiotherapy in patients with D5PSS 4 per central review. (F) Overall survival among patients with Deauville 5-point scale score 5 by response status based on conventional imaging (complete or partial remission vs stable or progressive disease). (G) Suggested algorithm for the treatment of patients with PMLBCL treated with R-da-EPOCH according to the results of EoT-PET/CT and the conventional (CT-based) response status. CT = computed tomography; D5PSS = Deauville 5-point scale score; EoT = end-of-treatment; PET = positron emission tomography; PMLBCL = primary mediastinal large B-cell lymphoma; R-da-EPOCH = rituximab and dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin.

Table 1

EoT-PET Characteristics, Central Review, Further Treatment, and Outcomes in Patients With Deauville Score 4 and 5 Positive Post-R-da-EPOCH PET/CT (n = 39; Listed by Increasing SUV_{max} in Post-R-da-EPOCH PET/CT)

	Post-R-da-EPOCH EoT-PET/CT						
Patient[a]	D5PSS (Local)	SUV_{max}	SUV_{max}/ SUV_{liver}	D5PSS at review	Post-R-da-EPOCH Treatment	Progression Status (mo Post EoT-PET/CT)	Vital Status (mo Post-R-da-EPOCH Initiation)
D4-1	4	2.5	1.04	3	No	CCR	ACR (68)
D4-2	4	2.9	1.44	4[b]	RT	CCR	ACR (83)
D4-3	4	3.0	1.36	3	No	CCR	ACR (64)
D4-4	4	3.3	1.03	3	No	Relapse (10)	ACR (43)
D4-5	4	3.4	1.42	4	No	CCR	ACR (73)
D4-6	4	3.6	1.57	4	No	CCR	ACR (64)
D4-7	4	3.8	1.15	3	No	CCR	ACR (31)
D4-8	4	3.8	1.31	4	No	CCR	ACR (31)
D4-9	4	3.9	1.22	3	No	CCR	ACR (56)
D4-10	4	3.9	1.44	4	No	CCR	ACR (56)
D4-11	4	3.9	1.39	4	RT	CCR	ACR (56)
D4-12	4	4.0	1.08	3	No	CCR	ACR (34)
D4-13	4	4.2	1.91	4	No	CCR	ACR (38)
D4-14	4	4.3	1.34	3	RT	CCR	ACR (71)
D4-15	4	4.5	1.80	4	No	CCR	ACR (42)
D4-16	4	4.6	1.77	4	No	CCR	ACR (76)
D4-17	4	4.6	2.30	4	No	CCR	ACR (38)
D4-18	4	4.8	2.18	4	RT	CCR	ACR (75)
D4-19	4	4.9	1.53	4	No	CCR	ACR (28)
D4-20	4	5.5	1.72	4	No	Relapse (8)	ACR (42)
D4-21	4	6.0	2.73	4[b]	RT	CCR	ACR (70)
D4-22	4	6.7	2.58	4	No	Relapse (2)	ACR (16)
D5R-1	5	7.7	3.50	NA	RT	CCR	ACR (34)
D5R-2	5	9.0	4.09	NA	RT	CCR	ACR (31)
D5R-3	5	10.4	>3	NA	RT	CCR	ACR (49)
D5R-4	5	11.7	>3	NA	RT	CCR	ACR (32)
D5R-5	5	11.7	>3	NA	RT	CCR	ACR (28)
D5P-6	5	12.8	>3	NA	ST/ASCTi	Event at STI (5)	ACR (56)
D5R-7	5	15.0	>3	NA	ST/ASCTi	Event at STI (6)	DOD (18)
D5P-8	5	16.0	>3	NA	ST/ASCTi	Event at STI (5)	ACR (37)
D5P-9	5	16.2	>3	NA	ST/ASCTi	Event at STI (5)	ACR (100)
D5P-10	5	18.2	>3	NA	ST/ASCTi	Event at STI (6)	DOD (26)
D5P-11	5	21.8	>3	NA	ST/ASCTi	Event at STI (5)	DOD (16)
D5P-12	5	22.5	>3	NA	ST/ASCTi	Event at STI (7)	DOD (10)
D5P-13	5	22.7	>3	NA	ST/ASCTi	Event at STI (6)	DOD (25)
D5P -14	5	22.9	>3	NA	ST/ASCTi	Event at STI (6)	AWD (8)
D5P-15	5	27.7	>3	NA	ST/ASCTi	Event at STI (5)	ACR (78)
D5P-16	5	NP	NP	NA	ST/ASCTi	Event at STI (5)	DOD (6)
D5P-17	5	NP	NP	NA	ST/ASCTi	Event at STI (3)	DOD (15)

[a]D4 = D5PSS-4 per local interpretation; D5R = D5PSS-5 responsive by conventional restaging; D5P = D5PSS-5 with progressive or stable disease (SD/PD) by conventional restaging.

[b]Unable to review according to D5PS.

ACR = alive in complete remission; AWD = alive with disease; CCR = continuous complete remission; DOD = died of disease; D5PSS = Deauville 5-point scale score; EOT = end-of-treatment; NA = not applicable; NP = not performed but considered as D5PSS-5 because of frankly progressive disease by conventional restaging; PD = progressive disease; PET/CT = positron emission tomography/computed tomography; RT = radiotherapy; ST/ASCTi = salvage therapy with the intention of autologous stem cell transplantation; STI = salvage therapy initiation; SUV = standardized uptake value.

a sizeable proportion of patients with D5PSS-4 does not need RT. However, it is not clear who are those who need it. In our real-life study, 22 of 141 (16%) patients had D5PSS-4 by local interpretation, but only 15 of 22 still had D5PSS-4 upon central review, generally with SUV_{max} > 1.4xSUV_{liver},[16] which could be a reasonable surrogate to define D5PSS-4 in everyday practice. Only 3 of 15 had SUV_{max} > 5 (5.6, 6.0, 6.7); 2 of 3 did not receive RT and both relapsed compared with 0 of 12 for those with SUV_{max} ≤ 5 (Table 1). Although patient numbers are small, these observations and others[8,21] support our initial data after R-CHOP+RT[4] and might justify the use of RT in D5PSS-4 with SUV_{max} > 5 (Figure 1G). How this compares with a strategy of close 6-week-PET/CT surveillance cannot be determined based on few available data. Furthermore, as D5PSS-5 is defined as uptake markedly higher than liver and/or new lesions, which might be interpreted as >2 or >3xliver,[15] some patients with high-uptake D5PSS-4 may be classified as D5PSS-5.

Important novel and clinically relevant data can also be derived regarding the 17 of 141 (12%) D5PSS-5 patients. RT can cure many patients with responding D5PSS-5 (PR by CT assessment), while the outcome is very poor for patients with progressive D5PSS-5 (SD/PD by CT), pointing out the need of novel treatment approaches for this small subgroup (11/141 or 8%).[22–24] This distinction is not typically made in published studies[8,9,21] and obviously requires a mid-treatment CT (or PET/CT) assessment. Interestingly, these 2 subgroups have highly different SUV_{max} values. Provocative data from the NCI/Stanford series suggest to avoid RT in D5PSS-5 patients as well, but 3 of 4 non-irradiated patients who did not progress had overlapping with SUV_{max} values with those already classified as D5PSS-4 in

the same study. It is very embarrassing for treating physicians to defer a potentially curative treatment in such cases, especially considering that the additional RT burden would be as low as 3.5% of all patients.

In conclusion, RT can be omitted after R-da-EPOCH and restricted to the small minority of patients with responding D5PSS-5 and high-uptake D5PSS-4 with SUV_{max} > 5, roughly corresponding to 6% of conventional responders, having in mind the very small likelihood of CNS relapse[17,18,25] or development of metachronous cHL.[19] Thus, rebiopsy at relapse following a negative EoT-PET is recommended. A suggested algorithm for the approach of patients treated with R-da-EPOCH based on EoT-PET and CT assessment is provided in Figure 1G.

AUTHOR CONTRIBUTIONS

TPV designed research, performed research, collected data, analyzed and interpreted data, performed statistical analysis, and wrote the article. AP performed research, collected data, analyzed and interpreted data and wrote the article. ZM, SGP, MPS, EH, ET, VPa, PT, AS, MBo, MBa, TK, and MKA designed research, performed research, collected data, analyzed and interpreted data. E. Verigou, EK, CK, CC, HG, DK, NP, LL, AnK, TL, VX, SK, EVr, GG, MP, MT, MK, GT, CP, TT, PZ, ArK, and DL collected data, analyzed, and interpreted data. VPr, SC, DD, ES, CM, and ID performed research, collected data, analyzed, and interpreted data. E. Verrou and VL collected data. HP designed research and performed research. PR designed research, performed research, collected data, analyzed and interpreted data, and wrote the article. All critically reviewed the article.

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