CANCER DIAGNOSIS & PROGNOSIS
4: 172-181 (2024) doi: 10.21873/cdp.10304

Clinical Outcomes in Patients With DLBCL Treated With R-CHOP According to Radiotherapy and Interim PET Response

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Abstract. *Background/Aim: Interim positron emission tomography/computed tomography (PET/CT) scan is a valuable tool for assessing the early metabolic response to chemotherapy in diffuse large B-cell lymphoma (DLBCL). Although radiotherapy is an effective treatment for lymphoma, especially for local tumor control, the role of consolidative radiotherapy in diffuse large B-cell lymphoma (DLBCL) remains controversial. This study analyzed the clinical outcomes of patients with DLBCL treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), stratified by interim PET response and the administration of radiotherapy. Patients and Methods: We conducted a retrospective review of 107 patients with DLBCL treated with R-CHOP chemotherapy between January 2012 and December 2016. Overall survival (OS), recurrence-free survival (RFS), and freedom from disease progression (FFDP) were calculated using the Kaplan–Meier method and compared using the log-rank test. Results: Forty-six patients were included in this analysis, with a median follow-up time of 65.9 months (range=4.7-125.3 months). The metabolic CR (mCR) group exhibited superior OS, RFS, and FFDP compared with the metabolic PR (mPR) group (p=0.003, p=0.001, and p=0.008, respectively). The 1-, 2-, and 5-year FFDP were 92.97%, 89.3%, and 85.6%, respectively, in the mCR group and 78.6%, 61.9%, and 44.2%, respectively, in the mPR group. In subgroup analysis, the FFDP of the mPR group without radiotherapy was significantly lower than that of the other groups (mCR with/without radiotherapy and mPR with radiotherapy, p=0.001). Conclusion: Consolidative radiation therapy using interim PET can benefit patients who do not achieve mCR. Further well-controlled prospective randomized trials are required.*

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Key Words: Diffuse large B cell lymphoma, interim PET/CT, consolidative radiation therapy, consolidation, radiotherapy, early response.

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodkin's lymphoma, is characterized by its aggressive clinical course (1, 2). The standard chemotherapy regimen for DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (3, 4). Although approximately two-thirds of patients achieve remission with first-line R-CHOP therapy, up to 30% face a poor prognosis if the initial treatment fails, even with salvage therapy (5-7).

For patients unresponsive to R-CHOP, radiotherapy emerges as a potential treatment option. In the rituximab era, studies evaluating the role of radiotherapy have produced conflicting results (8-10), attributed to reduced survival benefits from radiotherapy due to radiation-related toxicity and the heterogeneous nature of DLBCL. Given recent

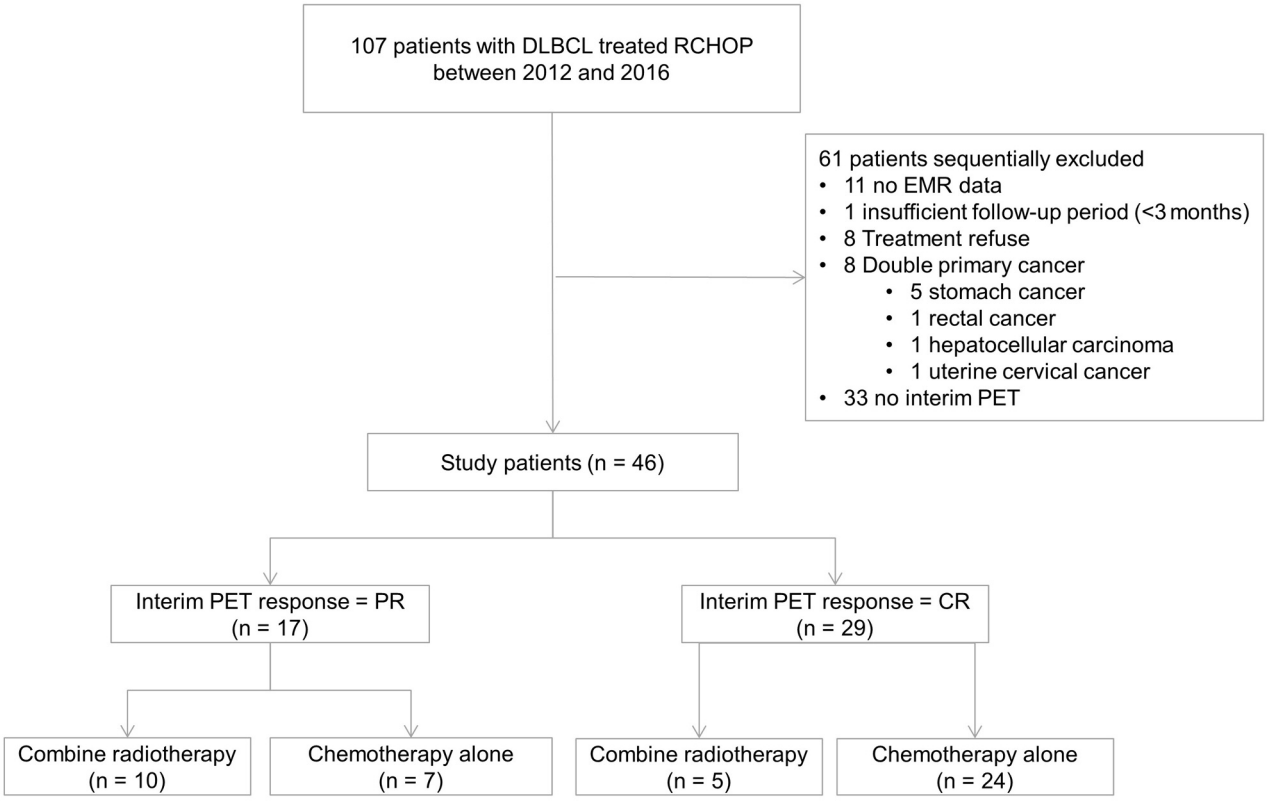

Figure 1. *Flow diagram. DLBCL: Diffuse large B-cell lymphoma; RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; EMR: electronic medical record; PET: positron emission tomography; PR: partial remission; CR: complete remission.*

developments in radiotherapy techniques, current treatment strategies employing smaller target volume contours and radiation dose reduction therapy are anticipated to further diminish radiation-related toxicities (11-13). Therefore, we posit that the incorporation of optimized radiotherapy in selective patients with DLBCL will result in improved clinical outcomes.

Meanwhile, F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) imaging can assist in the detection, staging, and remission assessment of patients with DLBCL (14, 15). In recent years, numerous studies have demonstrated that patients negative for 18FDG-PET (interim PET; iPET) during treatment exhibit superior clinical outcomes compared with patients who are iPET-positive (15, 16). We hypothesized that the efficacy of radiotherapy would vary depending on iPET results (iPET-negative or iPET-positive). However, limited information is available on how the incorporation of radiotherapy based on iPET results influences the oncological outcomes of DLBCL. This study aimed to stratify patients according to whether or not they received radiotherapy and iPET response and to compare oncological outcomes.

Patients and Methods

Study population. We performed a retrospective review of 107 patients with DLBCL treated with R-CHOP at our hospital between January 2012 and December 2016. The inclusion criteria were as follows: (a) histologically proven DLBCL; (b) age ≥18 years; (c) receipt of first-line R-CHOP chemotherapy; (d) underwent baseline PET-CT; and (e) underwent iPET scan after two or three cycles of R-CHOP chemotherapy. Exclusion criteria included: (a) double primary cancer; (b) negative baseline PET-CT; (c) incomplete R-CHOP chemotherapy with <6 cycles; and (d) insufficient follow-up duration (<3 months). Ultimately, 46 patients were included in the analysis (Figure 1).

This study received approval from the Kosin University Gospel Hospital Ethics Committee and Review Board, and the requirement for informed consent was waived owing to the retrospective nature of the study.

Treatment. Chemotherapy. All patients received six cycles of R-CHOP, consisting of rituximab (375 mg/m^2 on day 1, then every 3 weeks), cyclophosphamide (750 mg/m^2 intravenously on day 1), doxorubicin (50 mg/m^2 intravenously on day 1), vincristine (1.4 mg/m^2, ≤2.0 mg intravenously on day 1), and prednisolone (100 mg daily, orally on days 1 to 5, every 3 weeks).

Radiation therapy. Each patient was positioned in supine position and immobilized using a vacuum cushion. CT with intravenous

contrast enhancement (GE LightSpeed RT; GE Healthcare, Waukesha, WI, USA) was employed. The CT slice thickness was set at 2.5-5 mm. Delineation of the gross target volume was aided using CT, magnetic resonance imaging MRI, and PET. In some patients, a clinical target volume covering the adjacent nodal area in the same axial section as the gross tumor volume (GTV) was established. The planning target volume included a 5-7 mm margin from the GTV or clinical target volume. Radiation therapy underwent verification with kV imaging guidance using an onboard imager (Varian Medical Systems, Palo Alto, CA, USA) once or twice weekly. Setup corrections were based on anatomical landmarks, including bones and organs. Radiation therapy was administered using 6-10 MV X-rays from a linear accelerator (Clinac IX; Varian Medical Systems).

PET-CT imaging. FDG PET-CT scans were performed thrice using the same imaging protocol and PET-CT: at baseline, after two or three cycles (iPET), and upon completion of six cycles of RCHOP chemotherapy. All patients fasted for ≤6 h before the FDG PET/CT scan, and serum glucose levels were measured before F18-FDG injection. Prior to the PET scan, non-contrast-enhanced CT (3 mm slice thickness) was performed for anatomical co-registration. FDG (370-444MBq) was injected intravenously, and scanning commenced 50-70 min later using a Siemens Biograph mCT-64 PET/CT scanner (Siemens Healthcare, Knoxville, TN, USA). PET images were acquired in three-dimensional mode with an acquisition time of 3 min for each table position and 1.5 min for each bed position. Iterative reconstruction of PET images was performed with ordered subset expectation maximization, and attenuation-correction was performed using CT-derived transmittance maps. In our study, a complete metabolic remission (mCR) was defined as FDG uptake in DLBCL lesions indistinguishable from that in adjacent normal tissue.

Statistical analysis. To compare clinical factors between patients with and without metabolic remission on iPET, the *t*-test was employed for continuous variables, whereas the chi-square test or Fisher's exact test was used for categorical variables. Overall survival (OS) was estimated from the date of diagnosis to the date of death or the last follow-up, and recurrence-free survival (RFS) and freedom from disease progression (FFDP) were estimated from the date of diagnosis to the date of tumor recurrence or the last follow-up. OS, RFS, and FFDP were calculated using the Kaplan–Meier (KM) method and compared using log-rank tests. Univariate and multivariate analyses were conducted using a Cox proportional hazards model. Backward-elimination Cox regression was applied to select principal risk factors in the multivariate model. For all statistical tests, p-values <0.05 were considered statistically significant. All statistical analyses were carried out using R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients characteristics. Of 46 patients, 29 (63.0%) achieved mCR on iPET. The baseline characteristics of the patients are summarized in Table I. The mean tumor size was 9.5 cm in the metabolic partial remission (mPR) group and 5.8 cm in the mCR group, with this difference being statistically significant (p=0.005). Serum lactate dehydrogenase (LDH) levels were higher in the mPR group (82.4% *vs*. 75.9%, p=0.049). A higher percentage of patients in the mPR group received consolidative radiotherapy compared with the mCR group (58.9% *vs*. 17.2%, p=0.01). No statistically significant differences were observed between groups in terms of age, sex, ECOG scores, Ann Abor stage, extra-nodal disease status, IPI score, pretreatment SUVmax, and dose of radiation therapy.

Table I. *Patient characteristics according to interim metabolic response*.

Characteristics	Metabolic PR n=17	Metabolic CR n=29	*p*-Value
Age, year			>0.99
≤60	7 (41.2)	11 (37.9)	
>60	10 (58.8)	18 (62.1)	
Mean±SD	64.4±16.4	59.9±15.6	0.36
Sex			0.94
Male	8 (47.1)	12 (41.4)	
ECOG score			0.09
≤1	11 (64.7)	26 (89.7)	
Ann Abor stage			0.37
≤II	10 (58.8)	22 (75.9)	
>II	7 (41.2)	7 (24.1)	
Extra-nodal disease			0.89
Yes	3 (17.6)	7 (24.1)	
Serum LDH			0.049
Elevated	14 (82.4)	22 (75.9)	
Standard IPI			0.12
Low	3 (17.6)	15 (51.7)	
Low-intermediate	6 (35.3)	8 (27.6)	
High-intermediate	4 (23.5)	3 (10.3)	
High	4 (23.5)	3 (10.3)	
Revised IPI			0.16
Very good	1 (5.9)	4 (13.8)	
Good	8 (47.1)	19 (65.5)	
Poor	8 (47.1)	6 (20.7)	
Tumor size			0.022
<5 cm	4 (23.5)	19 (65.5)	
≥5 cm, <7 cm	2 (11.8)	1 (3.4)	
≥7 cm, <10 cm	1 (5.9)	3 (10.3)	
≥10 cm	10 (58.8)	6 (20.7)	
Mean±SD, cm	9.5±4.4	5.8±4.1	0.005
Pretreatment SUVmax			0.25
Mean±SD	15.4±7.3	12.7±7.0	
Radiation therapy			0.01
Yes	10 (58.9)	5 (17.2)	
Radiation therapy dose			
Mean±SD, Gy	33.6±5.1	39.2±6.4	0.08

Data are presented as number (%) of patients unless indicated otherwise. CR: Complete response; PR: partial response; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; IPI: international prognostic index; SUV: standardized uptake value.

Oncologic outcome. As of the October 2023 analysis, 30 (65.2%) patients were alive (mCR group, 23; mPR group, seven) and 16 patients had died, with a median follow-up

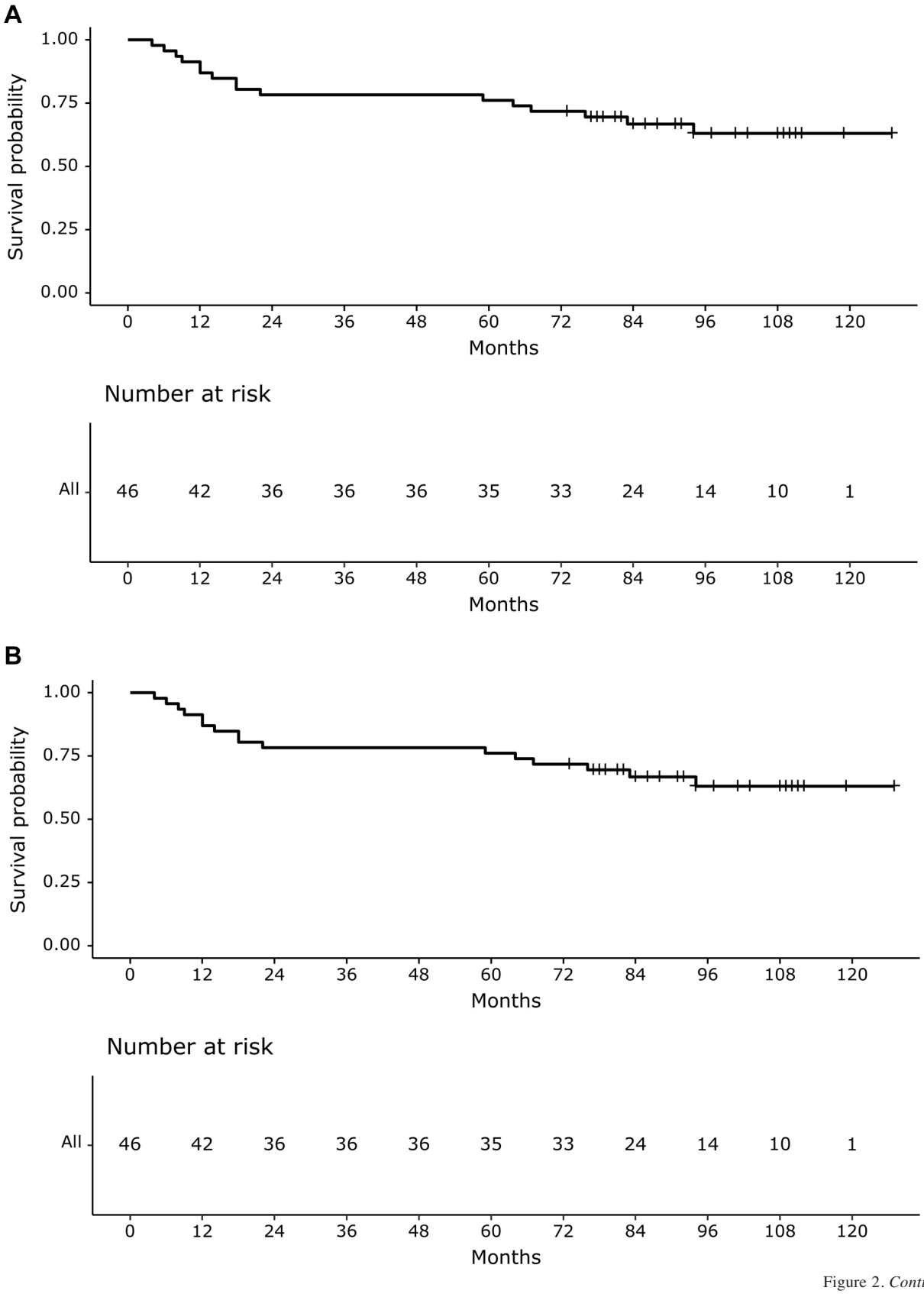

Figure 2. *Continued*

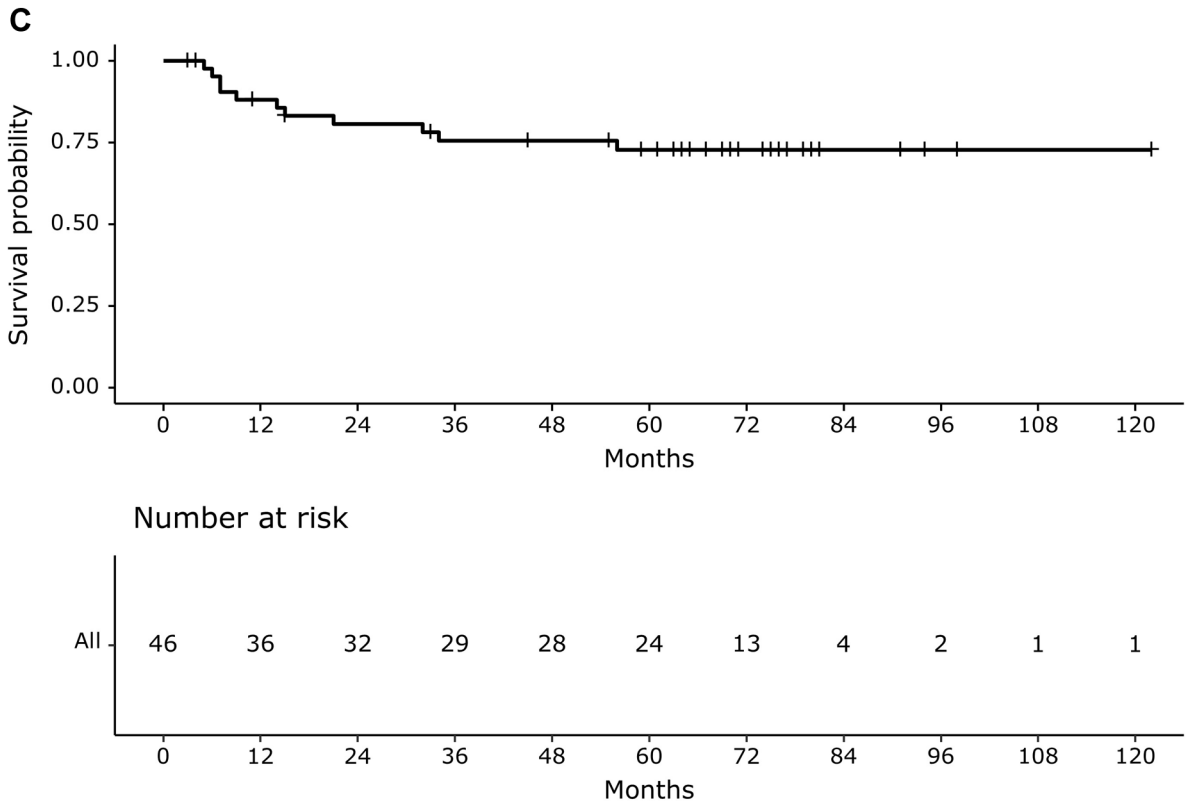

Figure 2. *Clinical outcome for all patients, by months of diagnosis. (A) Overall survival (OS), (B) recurrence-free survival (RFS), and (C) freedom from disease progression (FFDP).*

time of 65.9 months (range=4.7-125.3 months). The median time to OS, RFS, and FFDP was not reached. The mean OS was 94.3 months (Figure 2A). The RFS rates at 1, 2, and 5-years were 78.3%, 69.6%, and 60.9%, respectively (Figure 2B). Eleven patients experienced relapse after treatment, and the 1-, 2-, and 5-year FFDP rates were 88.1%, 80.7%, and 72.8%, respectively (Figure 2C). The mCR group exhibited superior OS, RFS, and FFDP compared with the mPR group (p=0.003, p=0.001, and p=0.008, respectively). The 1-, 2-, and 5-year OS rates according to the KM curve were 100%, 89.7%, and 86.2%, respectively, in the mCR group, and 64.7 %, 58.8 %, and 58.8 %, respectively, in the mCR group. The 1-, 2-, and 5-year RFS rates were 89.7%, 86.2%, and 79.3%, respectively, in the mCR group and 58.8 %, 41.2 %, and 29.4 %, respectively, in the mPR group (Figure 3A). The 1-, 2-, and 5-year FFDF were 92.97%, 89.3%, and 85.6% in the mCR group, and 78.6%, 61.9%, and 44.2% in the mPR group, respectively (Figure 3B).

In both the univariate and multivariate analyses, only mPR was associated with poorer OS (Table II) and FFDF (Table III). The multivariate analysis of RFS indicated that mPR (HR=0.164, 95%CI=0.062-0.434; p<0.001) and older age (HR=3.372, 95%CI=0.053-10.799) were associated with a decreased RFS. Similarly, in the multivariate analysis of RFS, mPR (HR=0.164, 95%CI=0.062-0.434; p<0.001) and age >60 (HR=3.372, 95%CI=0.053-10.799) were associated with poorer RFS (Table IV).

Subgroup analysis. To explore the impact of consolidative radiation therapy based on early treatment response to iPET, the data was stratified into four groups (Figure 1): Group A (mPR with consolidative radiation therapy), Group B (mPR without consolidative radiation therapy), Group C (mCR with consolidative radiation therapy), Group D (mCR without consolidative radiation therapy). Analysis of these four groups indicate that Group B exhibited significantly poorer FFDP than the other groups (Figure 4, p=0.001).

mCR group. The mPR group, with or without consolidative radiation therapy, and the mCR group, with or without consolidative radiation therapy, were compared. In the mCR group, no significant differences were noted in OS, RFS, or FFDP between patients who received radiotherapy and those who did not.

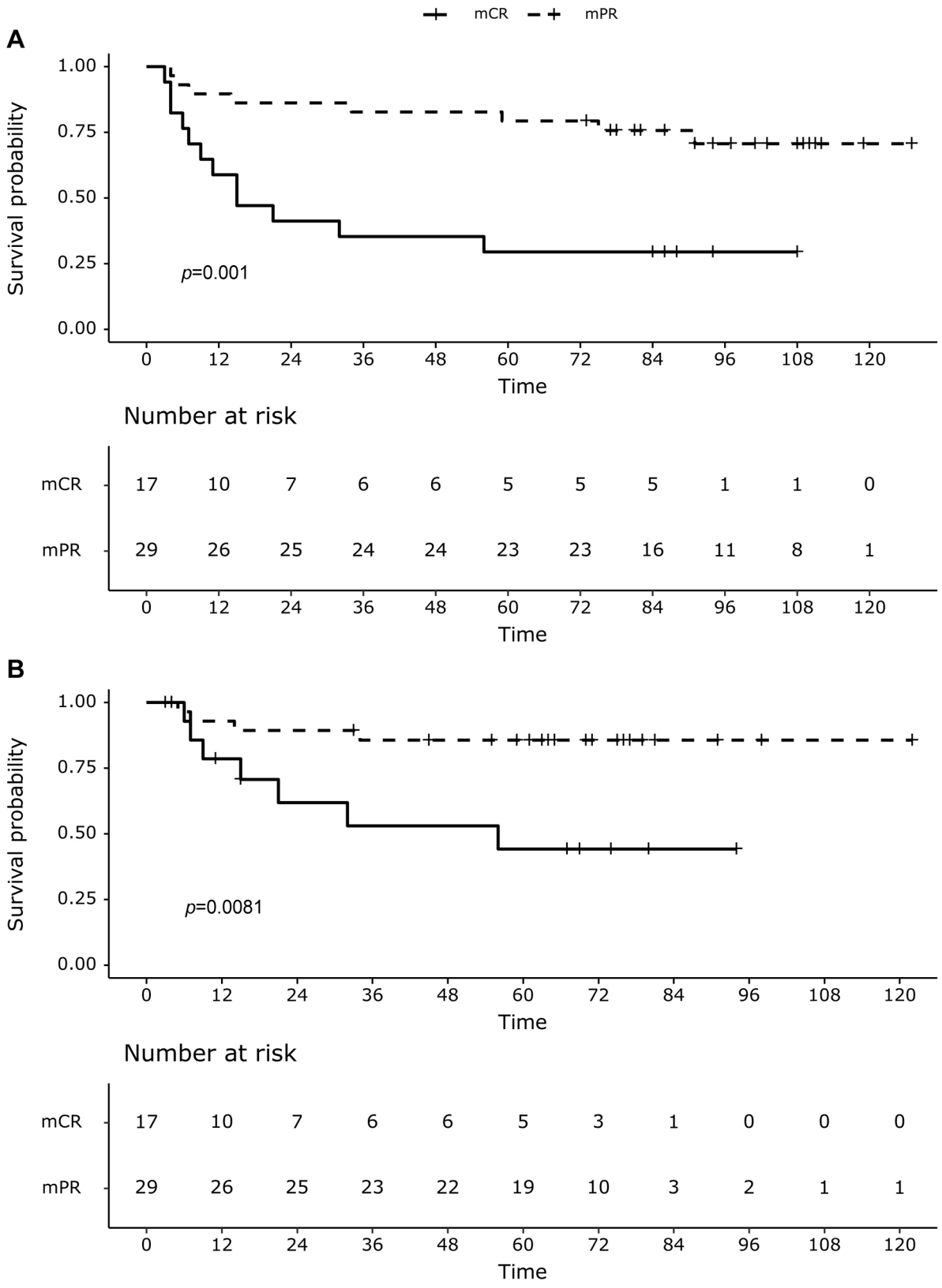

Figure 3. *Kaplan–Meier survival analysis for (A) recurrence-free survival (RFS) and (B) Freedom from disease progression (FFDP) stratified by interim positron emission tomography (PET) response [metabolic complete remission (mCR) vs. metabolic partial remission (mPR)].*

Table II. *Prognostic factor analysis for overall survival.*

	Univariate analysis			Multivariate analysis		
Variables (reference)	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (≤60)	3.155	0.898-11.078	0.07			
Sex (male)	1.203	0.447-3.236	0.71			
Ann Arbor stage (≤II)	2.242	0.829-6.065	0.11			
Extra-nodal disease (no)	0.559	0.194-1.611	0.28			
Serum LDH (normal)	2.585	0.831-8.039	0.10			
Interim PET response (PR)	0.242	0.088-0.672	0.006	0.218	0.078-0.609	0.003
Radiotherapy (no)	1.927	0.716-5.185	0.19			

HR: Hazard ratio; CI: confidence interval; LDH: lactate dehydrogenase; PET: positron emission tomography; PR: partial response.

Table III. *Prognostic factor analysis for freedom from disease progression.*

	Univariate analysis			Multivariate analysis		
Variables (reference)	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (≤60)	2.069	0.549-7.805	0.28			
Sex (male)	1.714	0.502-5.858	0.39			
Ann Arbor stage (≤II)	1.713	0.500-5.866	0.39			
Extra-nodal disease (no)	0.574	0.152-2.168	0.41			
Serum LDH (normal)	1.483	0.433-5.075	0.53			
Interim PET response (PR)	0.218	0.063-0.750	0.015	0.218	0.063-0.750	0.016
Radiotherapy (no)	0.930	0.246-3.516	0.91			

HR: Hazard ratio; CI: confidence interval; LDH: lactate dehydrogenase; PET: positron emission tomography; PR: partial response.

Table IV. *Prognostic factor analysis for recurrence-free survival.*

	Univariate analysis			Multivariate analysis		
Variables (reference)	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (≤60)	3.072	1.026-9.195	0.045	3.372	1.053-10.799	0.040
Sex (male)	1.429	0.583-3.501	0.43			
Ann Arbor stage (≤II)	2.505	1.030-6.096	0.042			
Extra-nodal disease (no)	0.405	0.161-1.019	0.05			
Serum LDH (normal)	1.956	0.750-5.100	0.17			
Interim PET response (PR)	0.242	0.097-0.602	0.002	0.164	0.062-0.434	<0.001
Radiotherapy (no)	1.260	0.502-3.163	0.62			

HR: Hazard ratio; CI: confidence interval; LDH: lactate dehydrogenase; PET: positron emission tomography; PR: partial response.

mPR group. Similar to the mCR group, the mPR group showed no significant differences in OS or RFS. However, in the subgroup analysis of FFDP, patients who received consolidative radiation therapy exhibited a trend that did not reach the threshold of statistical significance (p=0.052).

Discussion

Despite the improvement in oncological outcomes with the addition of rituximab to first-line chemotherapy, a subset of patients with DLBCL still require consolidation treatment. The

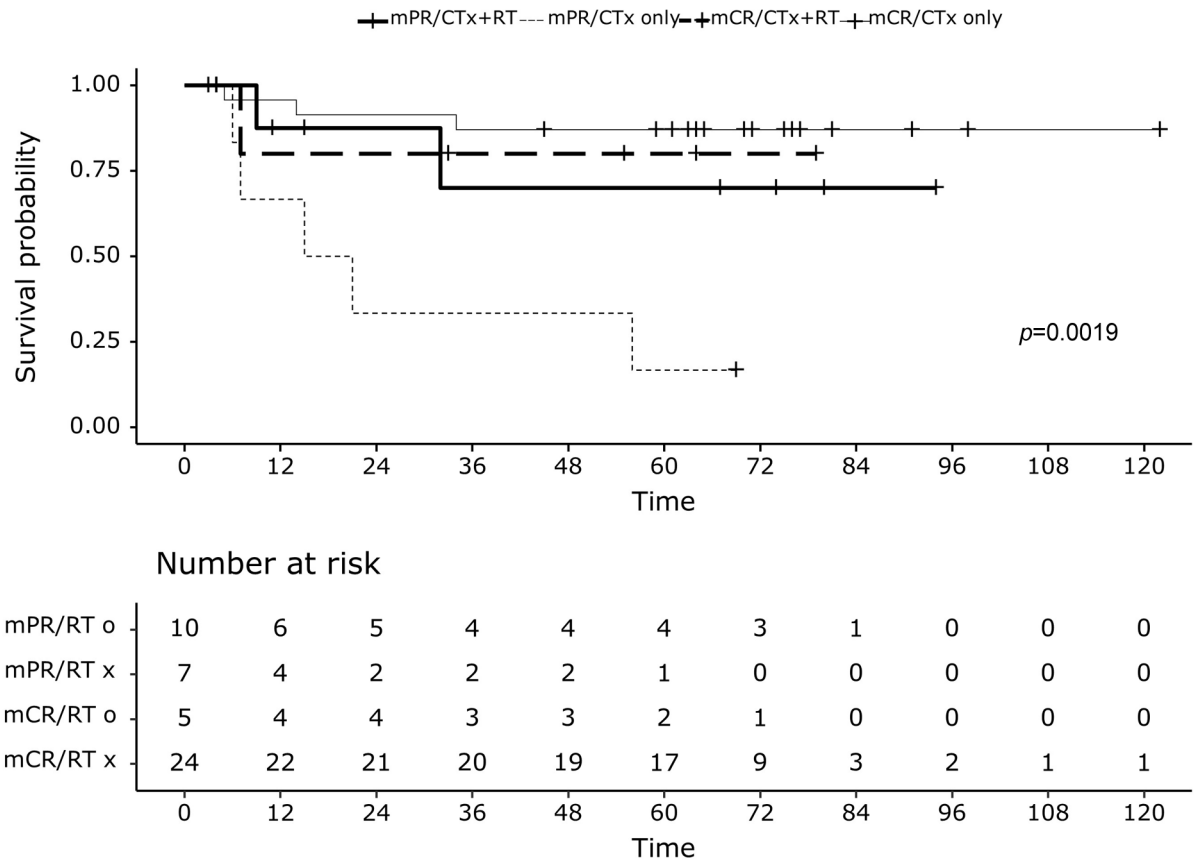

Figure 4. *Kaplan–Meier survival analysis for freedom from disease progression (FFDP) stratified by interim positron emission tomography (PET) response [metabolic complete remission (mCR) vs. metabolic partial remission (mPR)] and treatment [chemotherapy (CTx) + radiation therapy (RT) vs. chemotherapy only].*

role of consolidation radiation therapy in both pre-rituximab and rituximab eras remains a topic of debate. The concerns about the long-term toxicity of radiotherapy, including an elevated risk of secondary malignancies, have led to caution in its use (10, 17, 18). A multi-institutional study involving 334 patients with stage I-II non-bulky (<7 cm) DLBCL found no significant difference in OS between the R-CHOP and R-CHOP plus radiotherapy groups (p=0.28) (19). A meta-analysis that analyzed 11 trials of consolidation radiotherapy following chemotherapy (N=4,584) published from June 1966 to December 2018, indicated that there was no survival benefit when consolidation radiotherapy was given to unselected DLBCL patients following chemotherapy (20).

Contrary to the hesitation, some reports highlight the efficacy of consolidation radiation therapy in patients with DLBCL. Haque *et al*. (17) conducted a population-based propensity score matching study utilizing US Surveillance, Epidemiology, and End Results (SEER) data of patients with early stage DLBCL. They reported that patients who received radiation therapy demonstrated improved OS both before and after the rituximab era. Similarly, Phan *et al*. (9) reported in their study that consolidation radiation therapy after R-CHOP significantly improved OS and PFS in stage 1 or 2 DLBCL. The apparent contradiction in these results can be attributed to the high heterogeneity of DLBCL, including factors, such as immunophenotype, gene expression, and prognosis (21, 22). Building on the findings from the RICOVER-60 trial (23), where additional radiation therapy emerged as an independent prognostic factor for event-free survival (p=0.005), we posit that consolidation radiation holds promise for yielding favorable outcomes in a subset of patients with selective DLBCL.

Simultaneously, recent studies have underscored the independent prognostic value of the response on iPET in patients with DLBCL (24, 25). Furthermore, PET scan has proved valuable in early identification of "treatment non-responsive" patients with a poor prognosis (26).

According to the National Comprehensive Cancer Network (NCCN) guideline (version 6. 2023), it is recommended to consider radiotherapy after chemotherapy

in patients with stage I or II bulky disease (7.5 cm or more), especially in those with iPET PR. In advanced stages, consolidation radiotherapy is recommended for early bulky disease or isolated skeletal sites.

In our study, consolidation radiotherapy had no effect on oncologic outcome in all patients. However, subgroup analysis revealed that consolidative radiation therapy improved FFDP in patients who did not to attain metabolic remission on iPET. This result supports the NCCN guideline and the effectiveness of consolidation radiotherapy in selected patients. We contend that the decision to proceed with radiotherapy based on iPET scan findings has the potential to enhance clinical outcomes, particularly in individuals who do not achieve complete mCR on iPET CT.

Study limitations. This study has several limitations, primarily stemming from its retrospective design, introducing an inherent selection bias within the patient cohort. A major constraint was the small sample size obtained from a single institution. Consequently, we acknowledge that this analysis may have been insufficient to detect potentially subtle differences between subgroups because of the limited number of patients.

Conclusion

In summary, our data suggest potential benefits of consolidation radiation therapy for patients with DLBCL displaying mPR on iPET scans. We aspire to see our results serve as a foundation for future well-controlled, large-scale, and prospective randomized trials.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

J Yu, DJ Kim designed the study. SU Jung, JH Choi, and S Jun contributed data and data analysis. J Yu wrote the original draft of the manuscript. DJ Kim, HS Lee reviewed and edited manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Funding

This study was supported by a grant from the Kosin University College of Medicine.

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Received November 14, 2023
Revised December 17, 2023
Accepted December 18, 2023