Original article

Use of subsequent PET/CT in diffuse large B-cell lymphoma patients in complete remission following primary therapy

Xu Zhang[1,2], Wei Fan[1,2], Zhong-Jun Xia[1,3], Ying-Ying Hu[1,2], Xiao-Ping Lin[1,2], Ya-Rui Zhang[1,2], Zhi-Ming Li[1,4], Pei-Yan Liang[1,2] and Yuan-Hua Li[1,2]

Abstract

Interim ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (I-PET/CT) is a powerful tool for monitoring the response to therapy in diffuse large B-cell lymphoma (DLBCL). This retrospective study aimed to determine when and how to use I-PET/CT in DLBCL. A total of 197 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) were enrolled between October 2005 and July 2011; PET/CT was performed at the time of diagnosis (PET/CT0), after 2 and 4 cycles of chemotherapy (PET/CT2 and PET/CT4, respectively), and at the end of treatment (F-PET/CT). According to the International Harmonization Project for Response Criteria in Lymphoma, 110 patients had negative PET/CT2 scans, and 87 had positive PET/CT2 scans. The PET/CT2-negative patients had significantly higher 3-year progression-free survival rate (75.8% vs. 38.2%) and 3-year overall survival rate (93.5% vs. 55.6%) than PET/CT2-positive patients. All PET/CT2-negative patients remained negative at PET/CT4, but 3 were positive at F-PET/CT. Among the 87 PET/CT2-positive patients, 57 remained positive at F-PET/CT, and 32 progressed during chemotherapy (15 at PET/CT4 and 17 at F-PET/CT). Comparing PET/CT4 with PET/CT0, 7 patients exhibited progression, and 8 achieved partial remission. Comparing F-PET/CT with PET/CT0, 10 patients exhibited progression, and 7 achieved partial remission. In conclusion, our results indicate that I-PET/CT should be performed after 2 rather than 4 cycles of immunochemotherapy in DLBCL patients. There is a limited role for subsequent PET/CT in the detection of relapse in PET/CT2-negative patients, but repeat PET/CT is required if the PET/CT2 findings are positive.

Key words Interim PET/CT, diffuse large B-cell lymphoma, predictive value

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma, has a favorable prognosis. However, despite attempts to increase the efficacy of conventional chemotherapy during the past decade, approximately 40% of DLBCL patients still fail to respond to treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-like regimens. Current salvage therapy seems to be inadequate in insensitive patients; in the rituximab era, only 30% to 35% of patients who were treatment-resistant or relapsed had achieved prolonged progression-free survival (PFS) with high-dose chemotherapy followed by autologous stem cell transplantation[1]. A good strategy might be to identify patients with a poor prognosis early in treatment.

Interim ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (I-PET/CT) has been shown to be a powerful tool for monitoring the response to therapy in DLBCL[2-8]. Current guidelines recommend PET/CT only after completion of

Authors' Affiliations: [1]Collaborative Innovation Center for Cancer Medicine, State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, P. R. China; [2]Department of Nuclear Medicine, [3]Department of Hematological Oncology, [4]Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China.

Corresponding Author: Wei Fan, Department of Nuclear Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, P. R. China. Tel: +86-20-87343049; Fax: +86-20-87343681; Email: fanwei@sysucc.org.cn.

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first-line treatment because of the risk of false-positive findings[4]. Nevertheless, many lymphoma centers use routine surveillance PET/CT to ensure early detection of relapse, given the aggressiveness of this type of lymphoma. However, PET/CT is expensive, and there are no studies describing how to use it to monitor DLBCL patients during induction chemotherapy.

In this retrospective study, we analyzed a homogeneous cohort of newly diagnosed DLBCL patients treated with R-CHOP who underwent PET/CT at the time of diagnosis (PET/CT0), after 2 and 4 cycles of chemotherapy (PET/CT2 and PET/CT4, respectively), and at the end of first-line treatment (F-PET/CT) using the response criteria of the International Harmonization Project (IHP)[9] to interpret the scans. This study aimed to determine the predictive value of I-PET/CT in DLBCL patients and when and how it should be used.

Patients and Methods

Patient selection

This retrospective, single-arm study involved adult patients with histologically proven untreated DLBCL. The study was approved by the Ethics Committee at Sun Yat-sen University Cancer Center. The inclusion criteria were a pathologic diagnosis of *de novo* untreated DLCBL and age 18 years or over. Patients were excluded if they had human immunodeficiency virus (HIV) infection or a history of malignancy. Baseline assessment included bone marrow biopsy, full laboratory tests, HIV serology, and echocardiography. All patients had data available for PET/CT0, PET/CT2, PET/CT4, and F-PET/CT.

All patients were treated according to our departmental protocol. Depending on the stage and site of disease, the patients were given R-CHOP either alone or in combination with radiotherapy. All patients were treated with standard R-CHOP at 3-week intervals or dose-dense R-CHOP at 2-week intervals for 4, 6, or 8 cycles; therapy was performed as planned and was not altered due to the I-PET/CT findings unless progression occurred. Involved field radiotherapy was delivered to areas of bulky disease or FDG-avid areas. Follow-up data were recorded at scheduled visits.

^{18}F-FDG PET/CT

The patients were examined using a dedicated PET/CT system (Discovery ST-16, GE Health Care, Piscataway, NJ, USA). They were instructed to fast for 6 h and to abstain from caffeine and cigarettes for 24 h before the examination. ^{18}F-FDG (4.4–7.4 MBq/kg) was injected intravenously, after which the patient was requested to lie comfortably in a dark room for 60–90 min before the PET/CT scanning. The patients were scanned from the calves to the middle part of the femur while lying in a supine position. CT was performed before PET, and the resulting data were used to generate an attenuation correction map for PET. Two-dimensional PET images were reconstructed with a slice thickness of 3.25 mm using the ordered subset expectation maximization iterative image reconstruction method. PET, CT, and fused PET/CT images were generated for review on a Xeleris computer workstation.

Visual analysis of PET/CT images

All PET/CT images were analyzed by three experienced reviewers who were unaware of the clinical and follow-up data. The final PET/CT diagnosis was assigned by at least two reviewers. After all patients had undergone treatment, their PET/CT scans were designated as positive or negative according to the consensus response criteria of the IHP. In brief, a positive scan was defined as the presence of focal or diffuse FDG uptake above the mediastinal blood pool in a location incompatible with the normal anatomy and physiology, without a specific standardized cut-off value. A negative scan was defined as the absence of FDG uptake at any site of FDG-positive disease identified in the baseline study and lack of new FDG-positive disease[9].

The possible causes of false-positive scans were excluded. A more detailed set of instructions was created to address potential confounding variables, such as the interpretation of marrow FDG uptake, that required further clarification based on the reviewers' experience. These instructions were agreed upon by the reviewers before the review process was started[9].

Statistical analyses

Demographic and baseline disease characteristics were recorded. The primary end points were PFS and overall survival (OS) according to the IHP criteria. PFS was defined as the time from the start of treatment to the progression of lymphoma, death from any cause, or the last follow-up. OS was defined as the time from the start of treatment to death from any cause or the last follow-up. Survival was calculated according to the Kaplan–Meier method and compared between groups using the log-rank test. The complete response (CR) rates were compared between groups using Fisher's exact test. Differences were considered significant if the two-sided P value was < 0.05. All statistical analyses were performed using SPSS version 16.0.

Results

Patient characteristics

A total of 197 patients were enrolled between October 2005 and July 2011. The patient characteristics are summarized in **Table 1**. The median age of the patients was 46 years (range, 18–81 years); 48 (24.4%) patients were $\geqslant$ 60 years of age. Forty (35.5%) patients had International Prognostic Index (IPI) scores[10] indicating high-

Table 1. Characteristics of the 197 patients with diffuse large B-cell lymphoma (DLBCL)

Variate	Number of patients [cases (%)]
Sex	
Male	119 (60.4)
Female	78 (39.6)
Age ⩾ 60 years	48 (24.4)
Ann Arbor stage	
I	31 (15.7)
II	49 (24.9)
III	42 (21.3)
IV	75 (38.1)
IPI	
Low (0 or 1)	91 (46.2)
Low/intermediate (2)	36 (18.3)
High/intermediate (3)	15 (22.8)
High (4 or 5)	25 (12.7)
Chemotherapy	
R-CHOP-14	28 (14.2)
R-CHOP-21	169 (85.8)

IPI, International Prognostic Index; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP-14, R-CHOP regimen administered with a 14-day interval; R-CHOP-21, R-CHOP regimen administered with a 21-day interval.

intermediate or high risk (**Table 1**). The patients were followed up for 5–94 months, with a median of 30 months.

Treatment and outcome

Eighteen (9.1%) patients underwent surgery before chemotherapy; 191 (96.9%) patients completed 6 cycles of R-CHOP regardless of I-PET/CT findings. The chemotherapy plan was altered in 6 (3.1%) patients due to progression after 4 cycles of R-CHOP. Six (6.1%) patients underwent surgery at residual FDG-avid sites (1 due to inflammation, 1 with hepatic carcinoma, and 4 with lymphoma involvement) after 6 cycles of R-CHOP. Thirty-seven (18.8%) patients received combined modality therapy with 6 to 8 cycles of R-CHOP followed by involved field radiotherapy.

According to the IHP criteria, PET/CT2 scans were negative in 110 patients and positive in 87 patients. Among the 110 patients with negative PET/CT4 scans, 107 remained negative, but 3 had positive scans at F-PET/CT (**Figure 1A**). In 2 of the 3 F-PET/CT-positive patients, treatment had been delayed because of drug toxicity.

Among the 87 PET/CT2-positive patients, 19 were negative at PET/CT4, and 11 were negative at F-PET/CT; 57 remained positive at F-PET/CT. Thirty-two patients showed progression of disease during chemotherapy, 15 showed progression at PET/CT4, and 17 showed progression at F-PET/CT. Among the 15 patients who showed progression at PET/CT4, 6 had their treatment plan changed, and 2 achieved CR and remained alive at 37 and 48 months' follow-up. In the other 9 patients, treatment was considered to have failed; all of these patients had died by the end of follow-up, with a median survival of 13 months. Among the 17 patients whose disease had progressed at F-PET/CT, all had their treatment plan changed, and 4 (2 underwent radiotherapy, 1 underwent radiotherapy plus autologous stem cell transplantation, and 1 underwent surgery) achieved CR and remained alive at the end of follow-up (**Figure 1B**).

Of the 15 patients who showed progression at PET/CT4, only 7 were considered to have progressed when their PET/CT4 scans were compared directly with their PET/CT0 scans; the other 8 were considered to be in partial remission (PR) (**Figure 2**). Of the 17 patients who showed progression at F-PET/CT, 10 were considered to have progressed, and 7 were considered to be in PR compared with their PET/CT0 scans.

By the end of R-CHOP chemotherapy, 136 patients had achieved CR. The CR rate was significantly higher in scan-negative patients than in scan-positive patients at both PET/CT2 (97.3% vs. 33.3%, χ^2 = 46.400, P < 0.001) and PET/CT4 (96.9% vs. 16.2%, χ^2 = 135.74, P < 0.001).

At a median follow-up of 38 months (range, 5–94 months), 44

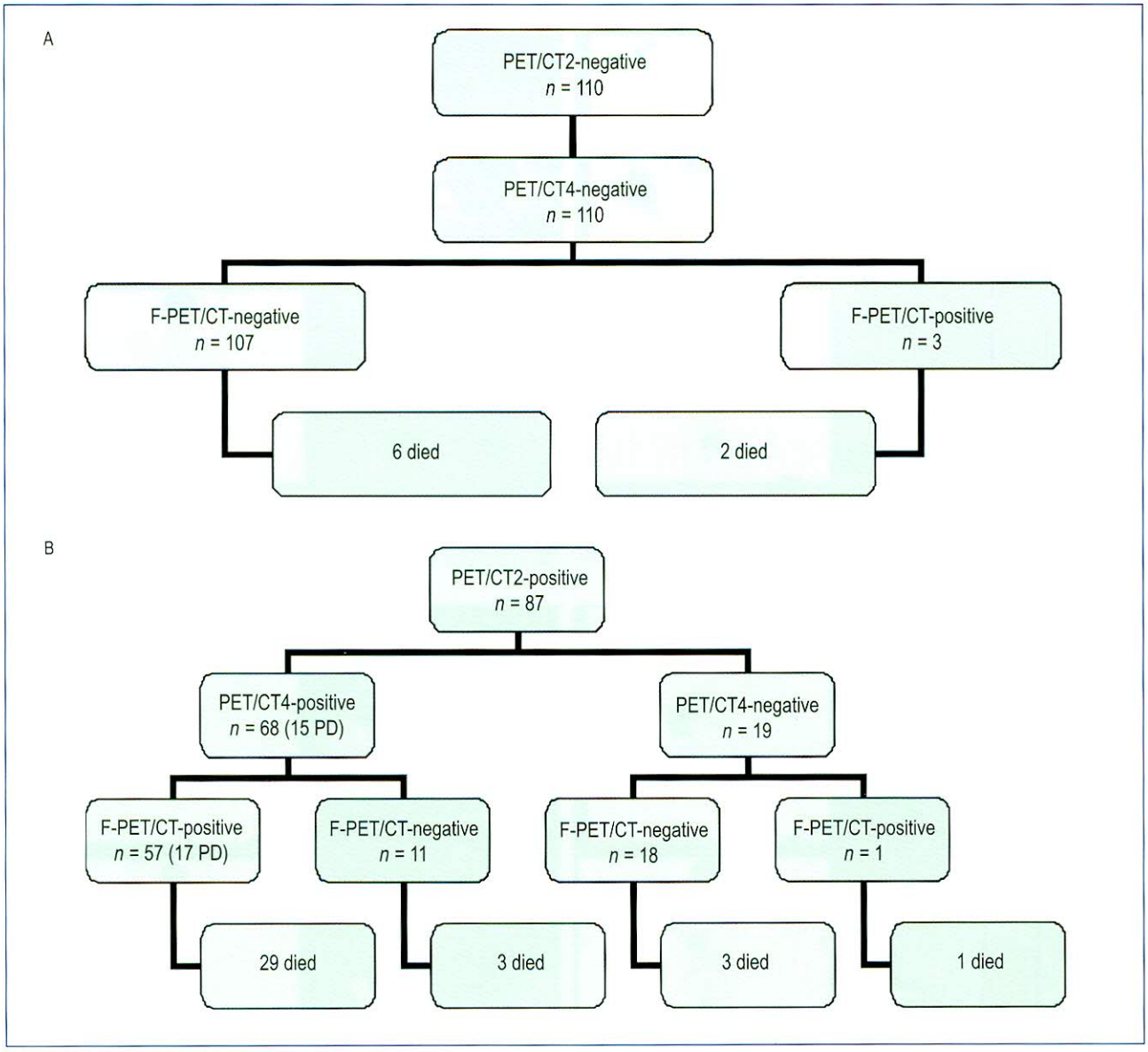

Figure 1. **Outcomes of the 197 patients with diffuse large B-cell lymphoma (DLBCL) according to findings on interim positron emission tomography (PET)/computed tomography (CT) after 2 cycles of chemotherapy (PET/CT2) and at the end of treatment (F-PET/CT).** A, outcomes of the 110 patients who had a negative PET/CT2 result after 2 cycles of chemotherapy. B, outcomes of the 87 patients who had a positive PET/CT2 result after 2 cycles of chemotherapy. PD, progressive disease.

patients had died from progressive disease (n = 39), infection (n = 3), heart failure (n = 1), or renal failure (n = 1). The OS rate of the study population was 77.3%.

Predictive value of PET/CT2 according to the IHP criteria

The 3-year PFS and OS rates were significantly lower in PET/CT2-positive patients than in PET/CT2-negative patients {PFS, 38.2% [95% confidence interval (CI) = 26.2%–50.2%] vs. 75.8% (95% CI = 68.3%–83.3%), χ^2 = 41.903, P < 0.001; OS, 55.6% (95% CI = 42.3%–68.9%) vs. 93.5% (95% CI = 88.8%–98.2%), χ^2 = 37.185, P < 0.001} (**Figure 3A** and **3B**).

Predictive value of PET/CT4 according to IHP criteria

The 3-year PFS and OS rates were also significantly lower in

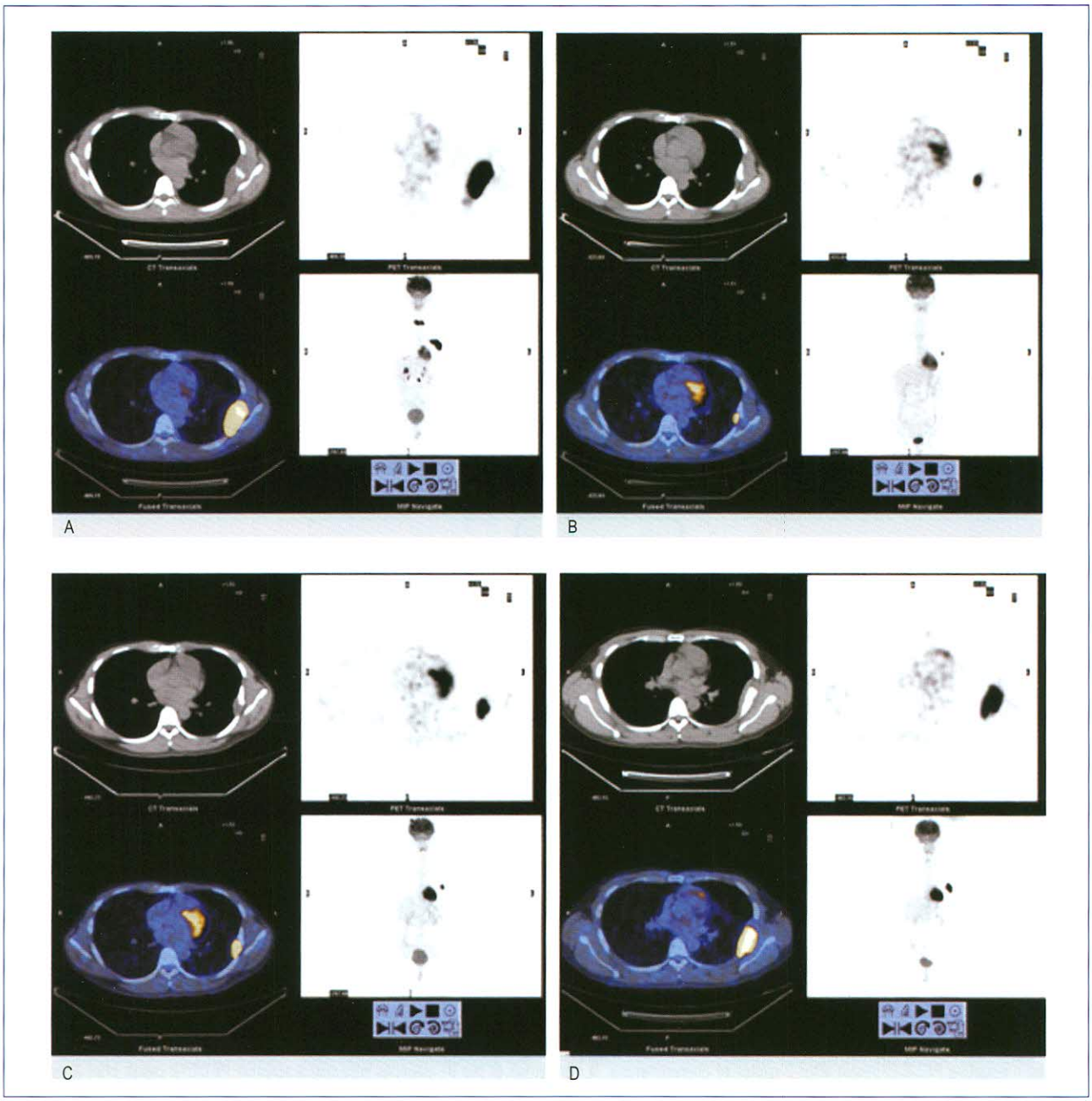

Figure 2. **PET/CT images before and after treatment.** A, PET/CT at diagnosis (PET/CT0); B, PET/CT after 2 cycles of chemotherapy (PET/CT2); C, PET/CT after 4 cycles of chemotherapy (PET/CT4); D, PET/CT at the end of treatment (F-PET/CT). If the PET/CT4 or F-PET/CT findings are compared with PET/CT0 alone, disease progression might be misinterpreted as partial remission. This patient received involved field radiotherapy after 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but the disease progressed and he died after 27 months.

PET/CT4-positive patients than in PET/CT4-negative patients [PFS, 24.7% (95% CI = 10.8%–38.6%) vs. 75.3% (95% CI = 67.8%–82.8%), χ^2 = 74.697, P < 0.001; OS, 49.4% (95% CI = 35.1%–63.7%) vs. 91.6% (95% CI = 86.5%–93.7%), χ^2 = 53.491, P < 0.001] (**Figure 3C and 3D**).

Discussion

The I-PET/CT manifestation during induction chemotherapy has been demonstrated to be an independent prognostic indicator in DLBCL, compared with pretherapeutic indices, such as IPI[7]. Interim

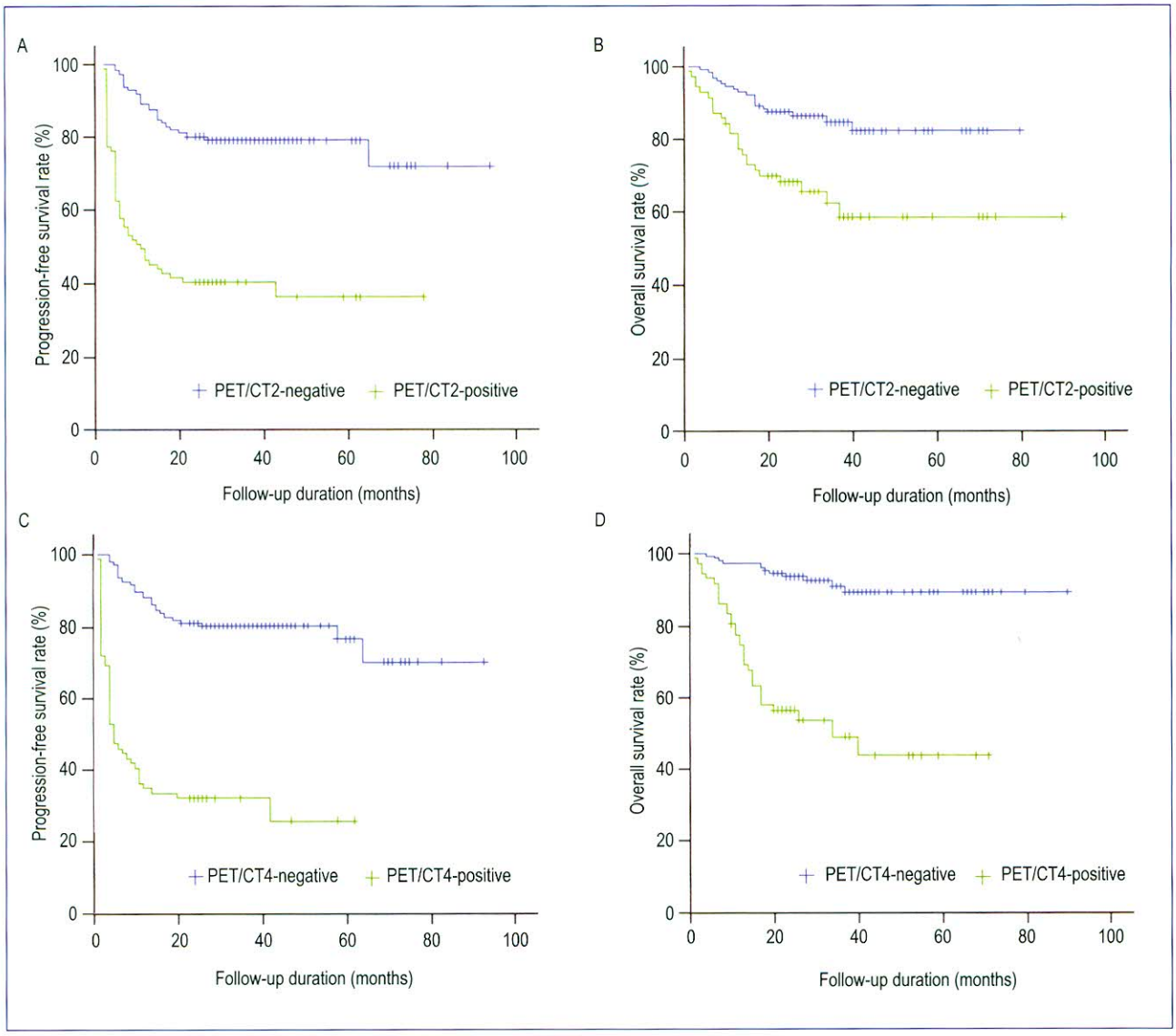

Figure 3. **The Kaplan-Meier survival curves based on PET/CT findings in 197 DLBCL patients.** A, progression-free survival (PFS) curves of PET/CT2-positive and -negative patients; B, overall survival (OS) curves of PET/CT2-positive and -negative patients; C, PFS curves of PET/CT4-positive and -negative patients; D, OS curves of PET/CT4-positive and -negative patients.

restaging is performed to identify patients whose disease has not responded to or has progressed despite induction therapy. However, previous studies have mainly included patients who underwent PET/CT during 2 to 5 cycles of chemotherapy, and these studies do not provide convincing evidence; furthermore, there is no consensus on how to monitor DLBCL patients during induction chemotherapy with first-line therapies[2-8]. Although the National Comprehensive Cancer Network (NCCN) guidelines do not recommend surveillance imaging for these individuals, PET/CT is widely used in clinical practice to monitor them. In the present study, we analyzed a homogeneous cohort of newly diagnosed DLBCL patients treated with R-CHOP who underwent PET/CT after every 2 cycles of chemotherapy, using the IHP consensus response criteria. Patients with negative PET/CT2 scans (n = 110) had significantly higher CR (97.3% vs. 33.3%), 3-year PFS (75.8% vs. 38.2%), and 3-year OS rates (93.5% vs. 55.6%) than those with positive PET/CT2 scans (n = 87). Patients with negative PET/CT4 scans still had higher CR (96.9% vs. 16.2%), 3-year PFS (75.3% vs. 24.7%), and 3-year OS rates (91.6% vs. 49.4%) than those with positive PET/CT4 scans.

Because cytotoxic chemotherapy is thought to kill cancer cells according to first order kinetics, after 2 cycles of chemotherapy in an idealized setting (assuming no interval tumor regrowth) one would

expect a 99.9% reduction in the number of viable cancer cells[11]. Most of the therapeutic effects occur upstream; therefore, an index that reflects reduced metabolism in the assessment of chemosensitivity is expected to be more discriminating after 2 cycles of chemotherapy than after 4 cycles. In our series, 110 patients had negative PET/CT2 scans, and 87 had positive PET/CT2 scans according to the IHP criteria. Of the 110 PET/CT2-negative patients, all had negative PET/CT4 scans. Among the 87 PET/CT2-positive patients, 15 showed progression of the disease at PET/CT4. However, if the PET/CT2 findings were disregarded, only 7 of these patients would be considered to have progressive disease by comparing their PET/CT4 scans with their PET/CT0 scans; the remaining 8 patients would be considered as being in PR. Following the NCCN guidelines, treatment may have been delayed in these 8 patients if they had not undergone PET/CT2. Our results indicate that I-PET/CT should be performed after 2 rather than 4 cycles of immunochemotherapy in DLBCL patients.

Because of the risk of disease relapse, many lymphoma centers use routine surveillance imaging, such as CT or PET/CT, to detect relapse early, given the aggressiveness of this type of lymphoma. However, less than one-third of recurrences are detected at an asymptomatic stage. Even intensive scheduled surveillance by PET/CT did not ensure the early identification of most recurrences, which were detected in the presence of pre-existing symptoms[12-15]. Interestingly, the outcome in asymptomatic patients appeared to be similar to that reported for symptomatic subjects[14,15]. In the present study, among the 110 patients with negative PET/CT2 scans, all remained negative at PET/CT4, and only 3 were positive at F-PET/CT. In 2 of these 3 patients, treatment had been delayed because of drug toxicity. For PET/CT2-negative patients, the CR rate reached 97.3%, and the 3-year PFS and OS rates were as high as 75.8% and 93.5%, respectively. DLBCL patients who survive this long are likely to have been cured. Thus, we believe that the role of subsequent PET/CT in patients with negative PET/CT scans after 2 cycles of chemotherapy is limited and that the current strategy increases the financial burden on these patients. Furthermore, repeated surveillance imaging increases patients' exposure to radiation and can potentially increase their risk of second malignancies[16,17]. One study has reported that routine surveillance imaging in long-term survivors of adult aggressive lymphoma exacerbates the underlying anxiety symptoms and fear of disease relapse or recurrence and negatively affects patient-physician communication[18].

I-PET/CT is performed to identify patients whose disease has not responded to or has progressed despite induction chemotherapy. However, I-PET/CT can give false-positive results, and some patients have a favorable long-term outcome despite a positive I-PET/CT scan. PFS in patients who were PET/CT4-positive and biopsy-negative was identical to that in PET/CT4-negative patients[5]. Therefore, I-PET/CT is not recommended for use in guiding decisions about changes to therapy[4]. In the present study, among the 87 PET/CT2-positive patients, 30 (34.5%) were negative at subsequent scans (19 at PET/CT4, and 11 at F-PET/CT). Although no biopsies were performed, a relatively large number of false-positive findings persisted. There are several potential explanations for false-positive scans. As a marker, ^{18}F-FDG does not have high specificity, and it is also taken up in infectious and inflammatory processes[19,20]. ^{18}F-FDG uptake after several cycles of chemotherapy may occur due to the presence of a persisting viable tumor or as a result of local inflammation[21]. It is also possible that the immunotherapy increased inflammation around the lesion. Antibody-mediated cellular cytotoxicity and complement activation are important mechanisms of action of rituximab[22,23], and both of these processes can attract inflammatory mediators to the tumor site. The variable use of rituximab in a minority of patients in previous studies, compared with its use in all of the patients in our study, may explain the high rate of FDG positivity unrelated to tumor activity[7,24].

Given the hypothesis that an early change in the treatment plan may lead to a greater number of cures in DLBCL patients, a strategy of treatment based on PET/CT performed at various time points during treatment could improve survival. In the present study, 15 patients with positive PET/CT2 scans showed progression of the disease at PET/CT4. Among these 15 patients, 6 had their treatment plans changed, and 2 of them achieved CR and remained alive at 37 and 48 months' follow-up. In the remaining 9 patients in whom the treatment plan was not altered according to the PET/CT4 findings, treatment was considered to have failed; all of these patients had died by the end of follow-up, with a median survival of 13 months. Although the number was small, some patients benefited from PET/CT-based treatment strategy. In our study, 36.8% (32/87) of the PET/CT2-positive patients showed progression of the disease during chemotherapy. Our results suggest that repeat PET/CT is needed if PET/CT findings are positive after 2 cycles of chemotherapy. Such a strategy would improve the management of patients with DLBCL, which we hope will translate into a longer survival time.

We acknowledge the limitations and potential biases of this study due to the retrospective collection of data and the relative disparity of the treatment types. In clinical practice, positive and negative criteria vary widely between individual nuclear medicine specialists, and only "negative" or "positive" was reported in this study; the hematologists did not know whether the patient's disease had progressed and could not adjust the treatment plan according to the I-PET/CT findings. Although PET/CT is a promising technique, reproducible and universal interpretation criteria are required to enable reliable conclusions to be drawn.

Conclusions

Our results suggest that I-PET/CT should be performed in DLBCL patients after 2 rather than 4 cycles of induction chemotherapy. There is a limited role for subsequent PET/CT for the detection of relapse in patients with negative findings after 2 cycles, but repeat PET/CT is needed if the scan after 2 cycles is positive.

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