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Summary
We report the analysis of 18F-fluorodeoxyglucose positron emission tomography/ computed tomography (PET/CT) scans in 88 patients with primary mediastinal lymphoma (PMBCL) treated using immunochemotherapy and radiation therapy in the IELSG-26 study. Patients who achieved a complete metabolic response (with Deauville score _3) all remain progression-free at 5 years, confirming the value of the Lugano classification criteria in the response assessment of PMBCL after radiation therapy. Patients with Deauville score 4 also had excellent outcomes. Thus, 18FDGPET/CT can identify patients at high risk of progression after radiation therapy.

Purpose: To assess the predictive value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for disease recurrence after immunochemotherapy (R-CHT) and mediastinal irradiation (RT), using the recently published criteria of the Lugano classification to predict outcomes for patients with primary mediastinal large B-cell lymphoma.
Methods and Materials: Among 125 patients prospectively enrolled in the IELSG-26 study, 88 were eligible for central review of PET/CT scans after completion of RT. Responses were evaluated using the 5-point Deauville scale at the end of induction R-CHT and after consolidation RT. According to the Lugano classification, a complete metabolic response (CMR) was defined by a Deauville score (DS) _3.
Results: The CMR (DS1, -2, or -3) rate increased from 74% (65 patients) after R-CHT to 89% (78 patients) after consolidation RT. Among the 10 patients (11%) with persistently positive scans, the residual uptake after RT was slightly higher than the liver uptake in 6 patients (DS4; 7%) and markedly higher in 4 patients (DS5; 4%): these patients had a significantly poorer 5-year progression-free survival and overall survival. At a median follow-up of 60 months (range, 35-107 months), no patients with a CMR after RT have relapsed. Among the 10 patients who did not reach a CMR, 3 of the 4 patients (positive predictive value, 75%) with DS5 after RT had subsequent disease progression (within the RT volume in all cases) and died. All patients with DS4 had good outcomes without recurrence.
Conclusions: All the patients obtaining a CMR defined as DS _3 remained progression-free at 5 years, confirming the excellent negative predictive value of the Lugano classification criteria in primary mediastinal large B-cell lymphoma patients. The few patients with DS4 also had an excellent outcome, suggesting that they do not necessarily

require additional therapy, because the residual ^{18}F-fluorodeoxyglucose uptake may not reflect persistent lymphoma. _ 2016 Elsevier Inc. All rights reserved.

Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) is a distinct clinicopathologic subtype of diffuse large B-cell lymphoma (DLBCL) arising from a small population of B cells within the thymic medulla (1-4).

Primary mediastinal large B-cell lymphoma usually occurs in the third to fourth decade of life, at a younger age than other DLBCL, with a female preponderance, and it

accounts for approximately 5% to 10% of DLBCL (2, 5-7). It is characterized by a rapidly progressive growth of anterior mediastinal mass, often with local invasion and compressive syndromes, and by recurrence at unusual extranodal sites (5, 6, 8).

Optimal treatment for PMBCL routinely includes multiagent immunochemotherapy (R-CHT), but the role of adjuvant radiation therapy (RT) remains controversial. Currently standard therapy comprises a combination of intensive doxorubicin-containing chemotherapy and rituximab (7, 9), and many centers include postchemotherapy irradiation as a routine part of the initial therapy. Retrospective studies (mostly performed in the pre-rituximab era)seem to indicate that the best outcomes are obtained whenconsolidation RT is given to the mediastinum. This choice isalso reinforced by the very poor outcomes for patients whodevelop recurrent disease, highlighting the need to achievecures at the first attempt (10-12). Nevertheless, mediastinalRT in young people carries a significant risk of long-termtoxicity, in particular second malignancies of the breastand lung and heart disease (13). Systemic R-CHT results incure in the great majority of patients, hence the routine consolidation RT is increasingly challenged, not least by excellent results in a small series of patients treated with the infusional DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, and doxorubicin plus rituximab) R-CHT regimen alone (14, 15).

The need for irradiation may be better defined by the use of 18F-fluorodeoxyglucose (18FDG) positron emission tomography/computed tomography (PET/CT), which allows evaluation of the metabolic response achieved after treatment. With numerous reports suggesting low risk of recurrence in patients with complete metabolic response (CMR), the British Columbia Cancer Agency has elected to omit RT for the patients who became 18FDG-PET negative at the completion of R-CHOP (chemotherapy regimens defined in Table 1 footnote), reducing the use of RT from 80% to 38% of patients, while maintaining excellent outcomes (16).

Hence, response evaluation is a particularly critical issue in defining the best treatment strategy in PMBCL, in which a residual mediastinal mass is frequently present at the end of R-CHT but only a minority of such masses apparently represent active disease. The IELSG-26 prospective study was conducted by the International Extranodal Lymphoma Study Group to gather information on some of the controversial issues in PMLBCL and to assess the accuracy of PET/CT to predict the outcome of patients with PMBCL treated with aggressive R-CHT regimens. This study showed that liver 18FDG uptake (Deauville score 3) is the best cut-off to define a CMR after R-CHT and to predict outcome (17).

However, the studies performed to date in PMBCL have not fully clarified whether RT might be avoided solely on the basis of a negative PET scan. The ongoing IELSG-37 randomized study (NCT01599559), led by the International Extranodal Lymphoma Study Group and designed with the aim of investigating the role of consolidation RT in patients who are 18FDG-PET negative at the end of R-CHT, may contribute to resolving this dispute.

At present RT is a widely used therapeutic option in patients with residual disease after R-CHT. In the present article we report the results of a new analysis to assess the value of postirradiation PET/CT in patients enrolled in the IELSG-26 study, in particular for those without a CMR after R-CHT.We analyzed the changes in the mediastinal PET findings after consolidation mediastinal RT, using the criteria of the Lugano classification (18).

Methods and Materials

Patient population

Between January 2007 and July 2010, 125 patients with pathologically proven PMBCL were prospectively enrolled in the IELSG-26 study (ClinicalTrials.gov identifier: NCT00944567) and treated with R-CHOP or R-CHOP-like, R-VACOP-B, or R-MACOP-B regimens according to local policy. Treatment details of 115 evaluable patients have been reported previously (17). Consolidation RT was given to 102 patients according to the local practice in the treating center. Six patients were not irradiated following the local policy of front-line treatment with R-CHT alone and 7 because of early progression requiring salvage therapy (Fig. 1). The study protocol included as mandatory for each center that the RT was irrespective of the PET findings obtained after R-CHT, the irradiation plan involved the original mediastinal tumor volume (involved-field RT, IFRT), the dose delivered was at least 30 Gy, and the beginning of the IFRTwas within 8 weeks of the last dose of R-CHT. After RT, patients were observed at monthly intervals for 3 months and then every 2 months until 1 year after treatment. Follow-up was every 3 months in year 2, every 4 months in year 3, every 6 months in year 4, and annually thereafter. Scans with PET/CT were performed after RT in 88 patients; the procedure was omitted in 10 patients because the protocol did not mandate scans in patients who had already attained a CMR at the end of R-CHT. Of the 4 remaining, 3patients had post-RT assessment by CT only, and 1 had disease progression during RT (Fig. 1). The study was conducted in accordance with the precepts of the Helsinki declaration and received approval by the local research ethics committee of each participating center.

18FDG-PET imaging procedures

The PET/CT scans were planned at baseline, within 14 days before commencing treatment, and 3 to 4 weeks after the end of the R-CHT. For patients receiving mediastinal irradiation, rescanning was scheduled after at least 2 months from the completion of IFRT. The PET/CT imaging was performed on full-ring integrated PET/CT systems. Each center was required to follow an active quality control and quality assessment protocol (19). Positron emission tomography and CT images were acquired in the same session. Computed tomography scans obtained with a low-dose protocol were used for attenuation correction of the PET images. All patients were fasted for at least 6 hours before the injection of 250 to 370 MBq (4.5 MBq/kg) of 18FDG. Blood glucose measured before injection of the radiotracer was <160 mg/dL in all patients. Positron emission tomography data were acquired in 2- or 3- dimensional mode from the mid-thigh toward the base ofthe skull after a standardized uptake time of 60 minutes (_5 minutes). The PET acquisition time was at least 3 minutes per bed position. Images were reconstructed with iterative algorithms according to the local protocols, and standardized uptake values were automatically calculated. For each examination the PET/CT image data were stored in Digital Imaging and Communications in Medicine format and sent, together with essential information, to the core laboratory for central review, which was performed after treatment by a single nuclear medicine physician (L.C.). Uncertain interpretations were resolved with the agreement of a second expert (L.G.). The review was blinded to the clinical information. The posteR-CHT and post-RT scans were visually assessed according to the Deauville criteria (20), with 18FDG uptake of any residual lesion scored according to the 5-point scale, using mediastinal blood pool (MBP) and liver uptake as reference settings. The achievement of a CMR was defined, according to the Lugano classification (18), by a completely PET-negative scan or a scan having minimal residual uptake less than or equal to the liver activity (Deauville score [DS] _3). Diffuse uptake in the spleen or marrow on the posteRCHT scan that was considered a result of chemotherapywas not scored as active disease.

Statistical methods

The outcome endpoints, overall survival (OS) and progression-free survival (PFS), were defined according to the revised National Cancer Institute criteria (21) and estimated by using the Kaplan-Meier or the life-table method, as appropriate (22). Differences between survival curves were analyzed using the log-rank test (23). The Mann-Whitney U test was used to test differences between variables in 2 groups of patients. P values of .05 or less (2-sided test) were considered to indicate statistical significance. Follow-up was calculated as the median time to censoring by using a reverse Kaplan-Meier analysis (24). The exact 95% confidence intervals (CIs) were calculated for incidence percentages. Negative predictive values and positive predictive values were calculated according to standard definitions (25). Statistical analysis was conducted using the STATA 11 software package (StataCorp, College Station, TX).

Results

The clinical characteristics of 88 patients included in the analysis are summarized in Table 1.
After the completion of R-CHT, all patients were planned and treated with a 3-dimensional conformal RT technique, with clinical target volume delineated on the CT simulation scan and involving the original mediastinal tumor volume, taking into account response to R-CHT and normal tissues displacement. The median interval between the end of R-CHT and the start of mediastinal RT was 43 days/6.1 weeks (interquartile range 34-52 days/4.8- 7.4 weeks). All patients received at least 30 Gy, with total doses ranging from 30 to 42 Gy (median 32 Gy and interquartile range 30-36 Gy) with 1.8- to 2-Gy daily fractions, without significant differences between patients with positive and negative PET scans (PET positive: 36 Gy, interquartile 31-36 Gy; PET negative: 31 Gy, interquartile 31-36 Gy; Mann-Whitney U test PZ.14). The median interval between the end of IFRT and the following PET scan was 84 days (2.75 months) (interquartile range 64-101 days/2.1-3 months). Also in this case no significant difference between patients with positive and negative PET scans was found (PET positive: 82 days, interquartile range 66-91 days; PET negative: 84 days, interquartile range 63-102 days; Mann-Whitney U test PZ.65). According to the Lugano classification, PET/CT visual assessment after IFRT showed CMR in 78 (89%; 95% CI 80%-94%) of 88 patients. In 34 patients (39%; 95% CI 28%-50%) the PET/CT scan was completely negative (score 1 according to the Deauville scale), and there were residual masses with 18FDG uptake less than MBP uptake (score 2) in 34 patients (39%; 95% CI 28%-50%) or higher than MBP uptake but below the liver uptake (score 3) in 10 patients (11%; 95% CI 6%-20%) (Fig.1).
A CMR was not attained in 10 (11%; 95% CI 6%-20%) of 88 patients, with a PET-positive residual mediastinal mass at the end of IFRT. In this group the residual uptake was slightly higher than the liver uptake (score 4) in 6 patients (7%; 95% CI 3%-14%) and markedly higher than the liver uptake (score 5) in 4 patients (5%; 95% CI 1%-11%). At a median follow-up of 60 months (interquartile range 51- 70 months), 5-year OS and PFS rates were 97% (95% CI 90%-99%). Three disease progressions within the RT volumeand classified as DS5 in all cases were recorded, and all resulted in death, despite salvage treatment with high-dose chemotherapy followed by autologous stem cell rescue. The remaining 7 patients with persistent PET positivity after IFRT (6 with DS4 and 1 with DS5) were managed expectantly with observation only and did not progress. Although in the study protocol additional PET/CT studies were not required during the follow-up, 5 of them (4 with DS4 and 1with DS5) underwent further PET scans demonstrating, at the local analysis, normalization of the FDG uptake in the residual masses after a delay between 2 and 30 months.
No patient with a CMR after IFRT has relapsed. All patients with DS4 had good outcomes without recurrence. The achievement of CMR after IFRT predicted significantly higher 5-year PFS and OS (100% vs 70%, log-rank test P<.0001 for both) (Fig. 2), with high sensitivity but limited specificity

(negative predictive value of 100% but positive predictive value of 30%). Comparing the PET results after R-CHT with those after mediastinal irradiation, the CMR (DS1, -2, or -3) rate increased from 74% (65 patients) after R-CHT to 89% (78 patients). Therefore 13 patients out of 23, 57% of the PETpositive patients after R-CHT, obtained CMR with mediastinal irradiation. All patients PET negative after R-CHT remained negative after IFRT (Fig. 1). The same comparative analysis showed a Deauville score reduced in 50 of 88 cases (57%), unchanged in 36 (41%), and increased in 2 patients (2%) but without change in the classification of the metabolic response.
Among the 3 patients who relapsed, 1 showed an increasing DS from 4 after R-CHT to 5 after IFRT, whereas in the remaining 2 cases the PET results were stably classified DS5.

Discussion

The IELSG-26 prospective study already provided the first validation of the Lugano classification criteria for the evaluation of the response to R-CHT in patients with PMBCL, where the CMR was defined as DS _3 (17). Despite some limitations due to its design (post hoc unplanned analysis on the subset of patients treated with combined modalities), the present study confirms the feasibility and utility of the Deauville 5-point scale for the response evaluation in patients receiving consolidation RT to the mediastinum after R-CHT. There are some particular aspects of post-IFRT PET scans in PMBCL that deserve further discussion. A CMR defined as DS _3 identifies almost all the patients projected to be alive and progression free at 5 years, confirming the excellent negative predictive value of the Lugano classification criteria in this population. Nevertheless, our results also confirmed the unsatisfactory specificity of the PET-positive scan (DS_4) after IFRT, something we already demonstrated in patients withPMBCL after R-CHT (positive predictive value 30% after IFRT vs 32% after R-CHT), although this was in the context of a reduced PET-positive rate (10% after IFRT vs 30% after R-CHT) (17). Subsequently, 2 retrospective studies showed analogous results of posteR-CHT PET in PMLBCL patients who then received consolidation RT (26, 27). In their retrospective analysis from the University of TexasMDAnderson Cancer Center published in 2015, Pinnix et al (26) demonstrated in a cohort of 97 stage I/II PMBCL treated with 1 of 3 main rituximab-containing regimens, with consolidation RT only given in 75% of cases, that all patients who experienced relapse or progressive disease had DS >3 after R-CHT. In all these patients salvage therapy (RT and autologous stem cell transplantation) was successfully applied. The authors concluded by suggesting that all patients with DS>3 after RCHTdeven after the R-EPOCH regimendshould be considered at high risk of relapse and, therefore, as candidates for further treatments beyond serial imaging and observation (26). On the other hand, Filippi et al (27) in a series of 51 PMBCL patients from the University of Turin, Italy, treated with a combined modality approach, showed that all 17 patients with posteR-CHT DS4 had an excellent outcome without relapse, too. Neither of these reports (26, 27) provided details on the post-RT PET evaluation of response in individual patients.
In the study by Filippi et al (27) all patients with post RCHT DS3 or DS4 were reported to attain a complete remission after RT. These remissions are assumed to have been clinically and radiologically documented because no information is given about metabolic response.
In our series, one-third of patients with DS4 before RT showed no changes in the PET uptake after irradiation, and when follow-up PET scans were repeated, they showed a subsequent improvement, in keeping with the clinical outcome in the series from Turin. In these cases the continued positive FDG uptake (DS4) after RT seems likely to reflect an inflammatory reaction due to the treatment rather than active disease. Indeed, their outcome was just as good as those with a reduction of uptake to DS _3. This finding importantly suggests that this subgroup of patients does not necessarily require salvage therapy. The design of our study does not, however, permit any conclusion on the role of RT, in particular for those who obtained CMR after R-CHT.

There is still a small subgroup of PMBCL patients with PET positivity after R-CHT who are not cured with RT. Our results revealed that patients with a DS5 after R-CHT are at significantly higher risk of progression anddeath (as depicted in Fig. 1, which summarizes the outcome of all the evaluable patients not achieving a CMR after R-CHT in the entire IELSG-26 study population, including those who were not irradiated and those who did not repeat a PET/CT scan after IFRT), particularly if this is not improved after RT. In fact, an FDG uptake of DS5 after RT, unchanged (3 cases) or increased (1 case) compared with the posteR-CHT result, showed a PPV of 75% (3 of 4 cases) for progression of disease and death. Further studies are warranted to identify this poorprognosis subset in advance, at a time when alternative approaches such as high-dose intensification with front-line autologous stem cell transplant are still a suitable option. Baseline quantitative PET parameters have been shown to be promising biomarkers for the design of risk-adapted therapeutic strategies in this setting (26, 28-31).

Conclusions

This study confirmed in a prospectively assembled series of PMBCL patients the excellent negative predictive value of the Lugano classification criteria. All patients who achieved a post-RT CMR (defined as DS _ 3) were indeed projected to be progression free at 5 years. The few patients with DS4 also had an excellent outcome, suggesting that they do not necessarily require additional therapy, because the residual FDG uptake may not reflect persistent lymphoma. This study confirms the value of the Lugano classification criteria in the response assessment in PMBCL and supports the use of 18FDG-PET to identify patients at high risk for progression after RT.

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Table 1. Baseline patient characteristics (n=88 unless otherwise specified)

Characteristic	n (%)
Age (y)	
Median (interquartile range)	34 (19-41)
≤60	84 (95)
Female sex	55 (62)
Performance status	
ECOG 0	40 (45)
ECOG 1	35 (40)
ECOG >1	13 (15)
B symptoms at presentation	33 (37)
Bulky disease	
Maximum mediastinal lesion >7 cm	74 (84)
Maximum mediastinal lesion >10 cm	43 (49)
Extramediastinal involvement ≥1 site	5 (6)
Bone marrow involvement	1 (1)
Ann Arbor stage	
I-II	80 (91)
III-IV	8 (9)
Serum LDH (>normal upper value)	65 (74)
IPI	
Low risk	69 (79)
Low-intermediate risk	17 (19)
Intermediate-high risk	2 (2)
High risk	0 (0)
aaIPI (n=84)	
Low risk	21 (25)
Low-intermediate risk	49 (58)
Intermediate-high risk	14 (17)
High risk	0 (0)
Front-line immunochemotherapy regimen	
R-CHOP 14	5 (6)
R-CHOP 21	4 (4)
Intensified R-CHOP	5 (6)
R-VACOP-B	47 (53)
R-MACOP-B	27 (31)

Abbreviations: aaIPI = age-adjusted International Prognostic Index; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-MACOP-B = rituximab plus methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; R-VACOP-B = rituximab plus etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

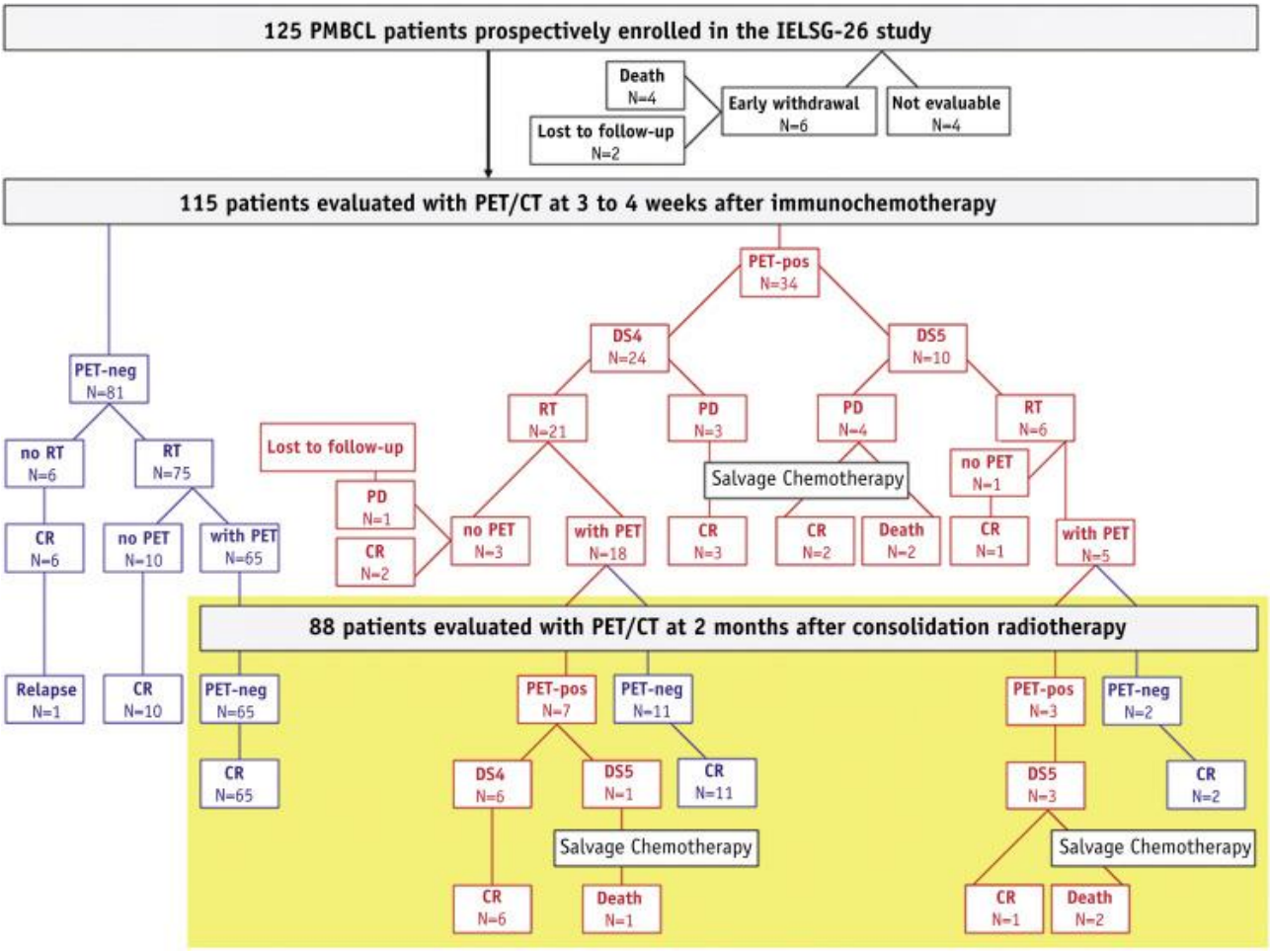

Fig. 1. Patient flow and outcome according to the positron emission tomography/computed tomography (PET/CT) remission status evaluated by using the Deauville score (DS) in the IELSG-26 study of primary mediastinal B-cell lymphoma (PMBCL). The subset of 88 patients treated with consolidation mediastinal radiation therapy (RT) who had a repeat PET/CT performed after irradiation are highlighted by the yellow rectangle. All the patients with DS ≤4 after RT achieved a long-lasting complete remission (CR). The chart also provides information on the outcome of the 34 patients not achieving a complete metabolic remission after immunochemotherapy, including those who were not irradiated and those who did not repeat a PET/CT scan after RT. Overall, 11 of 34 patients had disease progression, and 5 eventually died of lymphoma (1 was lost to follow-up after the progression). The frequency of progressive disease (PD) was significantly higher (Fisher exact test, *P*=.045) among patients with DS5 after immunochemotherapy (6 of 10 with PD, 60%) compared with those with DS4 (5 of 24 with PD, 21%).

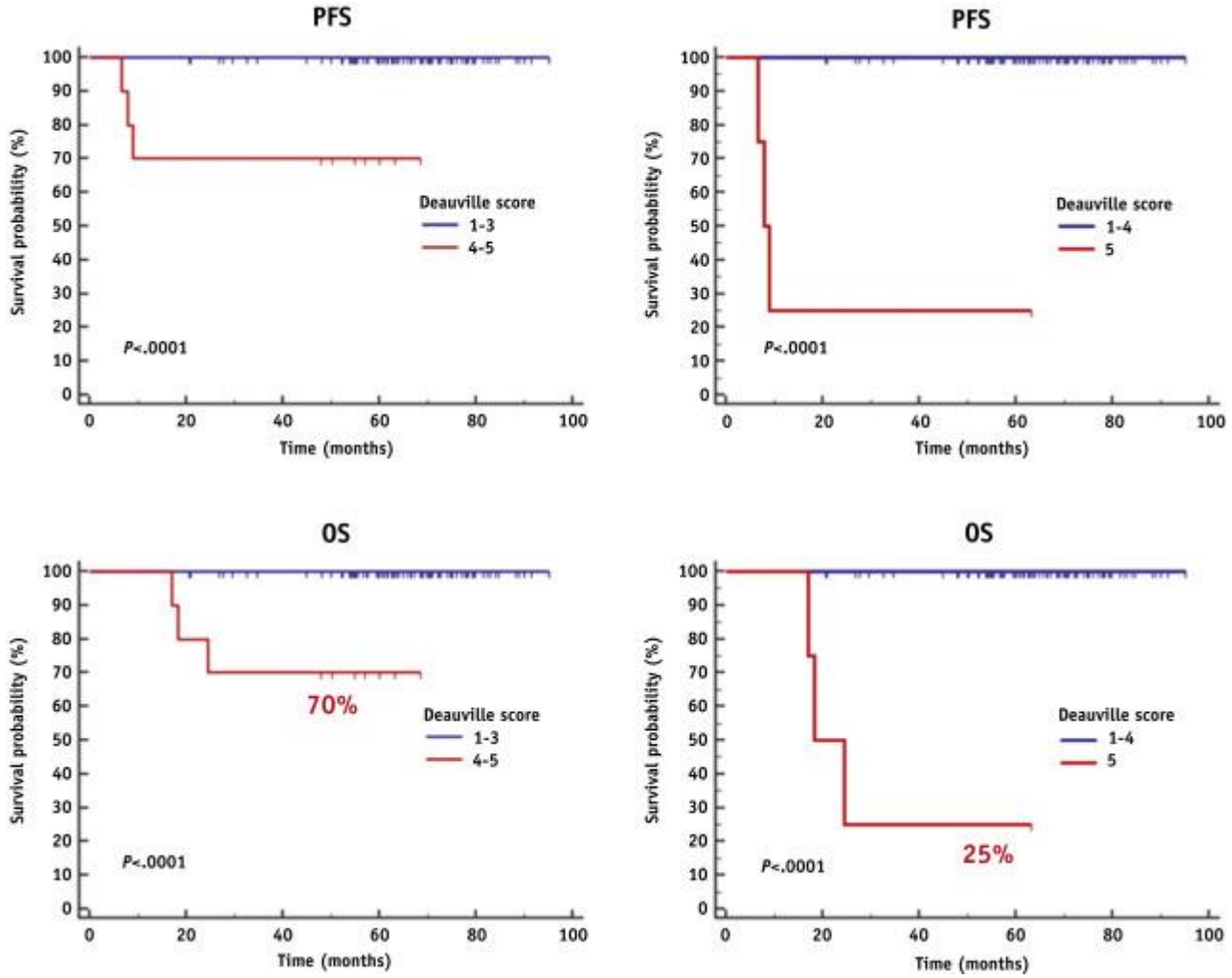

Fig. 2. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) in primary mediastinal large B-cell lymphoma according to the results of the post–radiation therapy positron emission tomography scans by using different ^{18}F-fluorodeoxyglucose uptake levels (Deauville score >3 vs Deauville score >4) as a threshold.