Radiation Therapy in Primary Mediastinal B-Cell Lymphoma With Positron Emission Tomography Positivity After Rituximab Chemotherapy

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Purpose

To investigate the role of radiation therapy (RT) in patients affected with primary mediastinal B-cell lymphoma (PMBCL) with residual ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET)-positive disease after rituximab chemotherapy (R-CT).

Methods and Materials

Thirty-seven patients treated with R-CT and RT, all with ^{18}FDG-PET scan at diagnosis and before RT, were included. All ^{18}FDG-PET scans were reviewed, and responses were classified according to the Deauville 5-point scoring system. Outcomes measures were overall survival (OS) and progression-free survival (PFS), estimated for the whole cohort and for subgroups according to ^{18}FDG-PET score after R-CT.

Results

The median follow-up time was 40.9 months. Three patients were assigned to Deauville score 1 (8.1%), 9 to score 2 (24.3%), 7 to score 3 (19%), 14 to score 4 (37.8%), and 4 to score 5 (10.8%). After RT, all patients with score 3-4 experienced a complete response (CR). Among patients with score 5, 1 was in CR (25%), 2 had persistent positivity (50%), and 1 showed progressive disease (25%). A total of 4 patients experienced progression or relapse: 1 of 33 (3%) with scores 1-4, and 3 of 4 (75%) with score 5. The 3-year OS and PFS of the whole cohort were 89.8% and 88.7%, respectively. OS was significantly different between scores 1-3 and scores 4-5 (100% vs 77% at 3 years, $P<.05$). Patients with a score of 5 had a significantly worse outcome than did all other patients (OS at 2 years, 33.3% vs 100%).

Conclusions

Approximately 50% of PMBCL patients show residual disease at ^{18}FDG-PET scan after R-CT. RT is able to convert to CR approximately 85% of these patients, but those with a Deauville score of 5 (10%) appear at high risk of progression and death, and they might be candidates for intensified programs.

Summary

Metabolic response after rituximab chemotherapy for primary mediastinal B-cell lymphoma is a key issue for optimizing treatment strategy. In this retrospective study we investigated the role of radiation therapy in patients with residual positron emission tomography positivity. The results show that radiation therapy is able to cure the majority of patients with residual active disease, but those with poorer metabolic response are at high risk of progression and death, and they might be candidates for intensified programs.

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) has been recognized as a distinct clinical entity, being an uncommon variant of diffuse large B-cell lymphomas (DLBCL) arising from thymic B cells 1 and 2. Single-institution or multiinstitution studies, mainly retrospective, showed that the combination of chemotherapy with CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) or CHOP-like regimens and radiation therapy (RT) is highly effective, given the peculiarity of the disease presentation and the tendency to

recurrence in the primary site of origin 3, 4, 5 and 6. In the rituximab era, current standard therapy is represented by a combination of chemotherapy (CHOP, CHOP-like, EPOCH - Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, M/VACOP-B - Methotrexate/Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone and Bleomicine) and rituximab followed by RT, with a higher response rate to rituximab chemotherapy (R-CT) when in comparison with chemotherapy alone 7, 8 and 9. Inasmuch as the outcomes are still unsatisfactory in a limited number of patients, with global overall survival rates of approximately 80%, more aggressive programs have been investigated, including strategies evaluating high-dose chemotherapy and autologous stem cells transplantation upfront (10). The need of consolidation RT has also been questioned in patients in complete remission after R-CT (11).

Response evaluation is a key issue in defining the best treatment strategy. In the past years, computed tomography (CT) or a combination of CT and ^{67}Gallium scans have been considered the gold standard. ^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) recently emerged as an important tool for chemosensitivity evaluation and response assessment in aggressive ^{18}FDG-avid lymphomas; its contribution in PMBCL management is therefore increasing, based on conventional response evaluation criteria defined for aggressive lymphomas and considering several limitations of morphologic radiologic findings in evaluating residual mediastinal tissue (12). A prospective international clinical trial lead by the collaborative International Extranodal Lymphoma Study Group, the IELSG 37 study (recently opened to accrual of patients) was designed with the aim of investigating the role of consolidation RT in ^{18}FDG-PET-negative patients. In this study, for ^{18}FDG-PET-positive patients (expected to be approximately 50%), the decision about further treatment is left to the treating physicians, underlining the uncertainty in the optimal management of patients with residual disease at functional imaging after R-CT. The introduction of an international validated scoring system for functional imaging interpretation, the Deauville 5-point system 13 and 14, might make it possible to better stratify patients on the basis of metabolic response, adapting the treatment strategy.

The aim of this retrospective study was to assess the role of RT in ^{18}FDG-PET-positive patients with various degrees of residual metabolic activity after R-CT.

Methods and Materials

A series of 37 patients with PMBCL, all evaluated with ^{18}FDG-PET at staging and restaging before RT and treated with R-CT followed by mediastinal RT, were included in the study.

All patients had histologically proven PMBCL; patients with grey-zone lymphomas or uncertainties between a diagnosis of PMBCL and DLBCL were excluded. Ann Arbor stage was I-II A/B in all patients. Bulky disease was defined as the presence of a mediastinal mass >10 cm in axial diameter. The detailed patients' characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristic	No.	%
Age, y		
Median	33	
Range	18-65	
Sex		
Male	15	40.5
Female	22	59.5
B symptoms	16	43.2
Bulky disease (>10 cm)	30	81.1
Deauville score 1	3	100

Characteristic	No.	%
Deauville score 2	7	77.8
Deauville score 3	6	85.7
Deauville score 4	10	71.4
Deauville score 5	4	100
LDH >450	29	78.4
aaIPI score		
0	3	8.1
1	18	48.6
2	16	43.3
Rituximab chemotherapy		
R-VACOP-B	15	40.6
R-CHOP 14	14	37.8
R-CHOP 21	8	21.6

Abbreviations: LDH = lactate dehydrogenase; aaIPI = age-adjusted international prognostic index; R-VACOP-B = rituximab-etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone.

Fifteen patients received R-VACOB-B (12 weeks), 8 patients R-CHOP21 (6 cycles every 21 days) and 14 patients R-CHOP14 (6 cycles every 14 days). The total number of rituximab infusions was 8 in all different schemes. The median time between the end of R-CT and ^{18}FDG-PET evaluation was 28 days (range, 10-36 days). All patients received RT after R-CT, with doses ranging from 27 to 40 Gy, in 1.8- to 2-Gy-daily fractions. The treating radiation oncologists prescribed the radiation dose according to morphologic and/or functional response. The clinical target volume (CTV) included the initial volume of the mediastinal mass at presentation, taking into account tumor shrinkage after R-CT and displacement of normal structures. The margins from CTV to planning target volume (PTV) depended on immobilization methods and on the eventual use of image guidance techniques (5 mm isotropic if daily cone-beam CT was used, 8 mm if not).

Twenty-five patients were planned and treated with 3-dimensional conformal RT, and image-guided intensity modulated RT was used in 12 patients. The median interval between the end of R-CT and the start of mediastinal RT was 53 days (range, 20-86 days).

^{18}FDG-PET/response assessment

All ^{18}FDG-PET scans were acquired from the orbits to the proximal third of the thighs. Scans were acquired on a Philips Gemini Tomograph or a General Electric Discovery ST scanner.

^{18}FDG-PET after R-CT was performed at a median interval of 28 days after the end of treatment (range, 10-36 days).

In patients with a positive scan before radiation therapy, ^{18}FDG-PET was repeated 3 months after the end of RT.

All patients fasted at least 6 hours before the intravenous injection of 37 MBq per 10 kg ^{18}F-glucose, and had glucose levels between 90 and 160 mg/dL at the moment of injection; all scans were acquired within a range of 60 to 90 minutes after injection.

Two expert nuclear medicine physicians retrospectively reviewed all ^{18}FDG-PET scans. For all scans, maximum standardized uptake value (SUV_{max}) of the liver and mediastinal blood pool (MBP) were obtained.

^{18}FDG-PET response assessment was evaluated by means of the 5-point scoring system (5-PS), a criterion for visual analysis defined at the First Consensus Conference in Deauville in 2009, with its use subsequently refined in the following yearly international workshops (14). The Deauville 5-PS is defined as follows: *(1)* no uptake; *(2)* uptake equal to or less than mediastinum; *(3)* uptake more than mediastinum but less than liver; *(4)* uptake moderately increased compared with the liver at any site; *(5)* uptake markedly increased compared with the liver at any site, new sites of disease, or both.

Response after R-CT and after RT was evaluated on CT scans, ^{18}FDG-PET scans, or both by using the 2007 revised response criteria for malignant lymphomas: complete response (CR), regression to normal size on CT or mass of any size if ^{8}FDG-PET result was negative; partial response (PR), ≥50% decrease in the sum of the products of the diameters of up to 6 largest dominant masses, no increase in size of other nodes, or 1 or more ^{8}FDG-PET positive results at previously involved site (12).

Statistics

The median follow-up time was calculated by using the reverse Kaplan-Meier method. The major endpoints of the study were overall survival (OS), calculated from diagnosis to death resulting from all causes at the last follow-up visit, and progression-free survival (PFS), calculated from the date of diagnosis to progression, relapse, and death of any cause at the last time of follow-up. Survival analysis was calculated with the Kaplan-Meier method, and the log-rank test was used to evaluate statistical differences. The limited number of events precluded a reliable calculation of both univariate and multivariate assessment for potential predictors of progression/recurrence. According to the preplanned analysis, we estimated OS and PFS for the whole cohort and then compared 2 subgroups of patients according to their Deauville score (1-3 vs 4-5, with OS and PFS as endpoints).

Results

The median follow-up time of the entire study population was 40.9 months (range, 9.6-121.4 months).

At CT scan, CR was obtained in 6 patients (16.2%) and PR in 31 patients (83.8%).

Three patients were assigned to Deauville score 1 (8.1%), 9 to score 2 (24.3%), 7 to score 3 (19%), 14 to score 4 (37.8%), and 4 to score 5 (10.8%).

Patients with scores 1-3 received a median RT dose of 31.7 Gy (range, 25.2-36 Gy); patients with scores 4-5 received a median dose of 35.3 Gy (range, 30-40 Gy).

The total number of patients with a functional negative finding after R-CT was 12 of 37 (32.4%) with a positivity cutoff value of 3, and was 19 of 37 (51.3%) with a positivity cutoff value of 4.

After RT, all 7 patients with Deauville score 3 and all 14 patients with Deauville score 4 obtained a CR with ^{18}FDG-PET negativity (100%). Among 4 patients with Deauville score 5, 1 obtained a CR (25%), 2 had persistent positivity (50%), and 1 showed progressive disease (25%), with the mediastinal mass increased in diameter at CT scan and with enhanced metabolic activity (SUV increased in comparison with the pre-RT imaging).

No differences were observed in response rate between different R-CT regimens.

Four patients experienced progression or relapse: 1 had a Deauville score 2 at the end of R-CT, and 3 had a score 5. The first patient experienced relapse at 6 months from the end of RT inside radiation fields; she then underwent salvage treatment with high-dose chemotherapy and autologous transplantation and then allogeneic transplantation, and is currently in stable disease. The other 3 relapses occurred in patients with a score of 5 and were as follows: 1 patient experienced relapse 5 months after obtaining a CR after RT (in field), 1 showed evident progression just after RT (in field and out of field), and 1 had experienced persistent disease and progression 5 months after RT (in field and out of field). All 3 patients experienced progression and died after several salvage treatments. Figure 1 shows in details the pattern of response and relapse. Table 2 shows the distribution of all patients' responses to R-CT according to the Deauville 5-PS and the morphologic criterion, with the corresponding number of events (relapses/progressions).

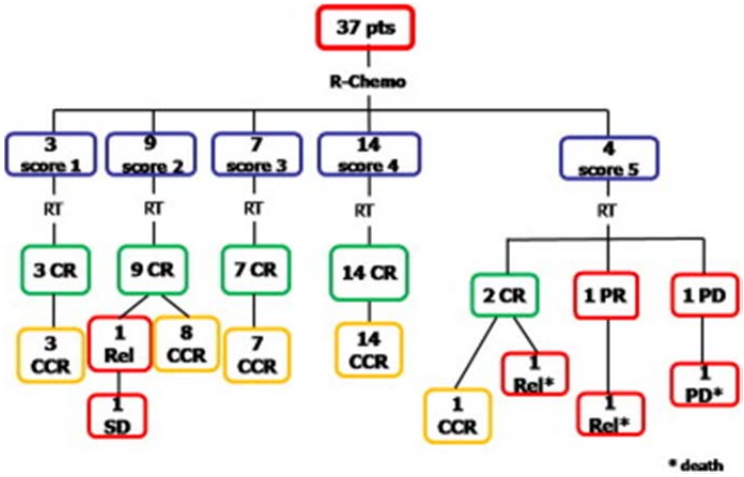

Fig. 1.

Pattern of response (according to Cheson's modified criteria) and relapse/progression. CR = complete response; PR = partial response; CCR = continuous complete remission.

Table 2.

Response to rituximab chemotherapy according to Deauville 5-point scoring system, matched with responses on computed tomography and number of relapses/progressions

No. of patients	PET Deauville 5-PS	Response at CT				No. of relapses/progressions
		CR	PR	SD	PD	
3	1	3	0	0	0	0
9	2	2	7	0	0	1
7	3	1	6	0	0	0
14	4	0	14	0	0	0
4	5	0	4	0	0	3
Total = 37		Total = 6	Total = 31	0	0	Total = 4

Abbreviations: CT = computed tomography; PET = positron emission tomography.

The 3-year OS and PFS rates of the whole cohort were 89.8% and 88.7%, respectively (Fig. 2).

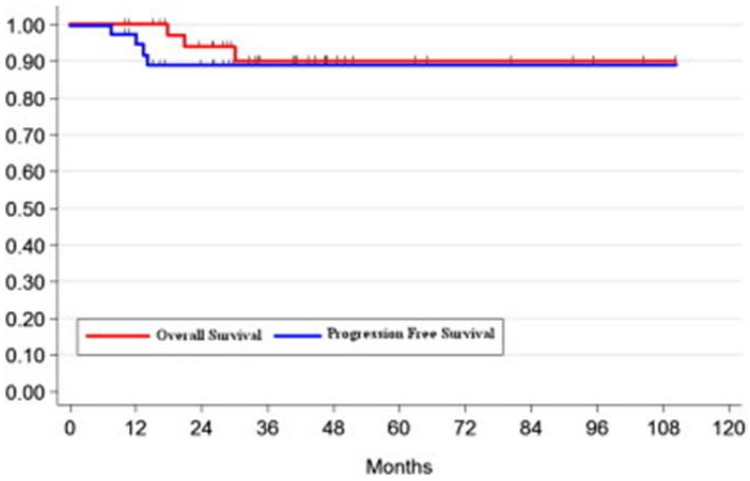

Fig. 2.

Overall survival and progression-free survival estimates for the whole cohort.

Patients with scores 1-3 had a significantly superior OS rate than did patients with scores 4-5: 3-year OS, 100% versus 77% (95% CI 43.2-92.2), *P*<.05; whereas there was no significant difference in PFS: 3-year PFS, 94.1% (95% CI 65-99.1) versus 83.3% (95% CI 56.8-94.3), *P*=.3 (Fig. 3).

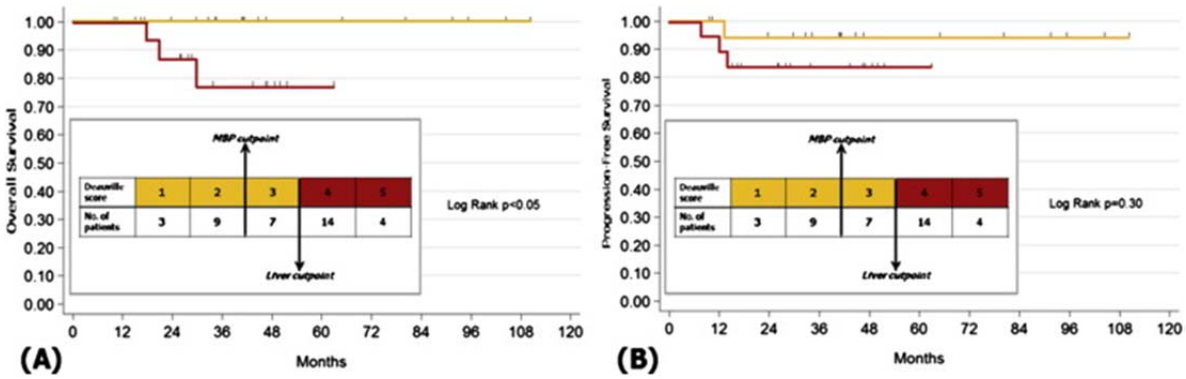

Fig. 3.

Overall (A) and progression-free (B) survival estimates by Deauville score (1-3 vs 4-5).

Because all events occurred in patients with a score of 5, we conducted an exploratory analysis comparing this subgroup of patients with all others. OS at 2 years for patients with scores 1-4 was 100%, and PFS at 2 years 96.8% (95% CI 79.2-99.5); for patients with score 5, OS rate at 2 years was 33.3% (95% CI 9-77.4), with a PFS rate at 1 year of 50% (95% CI 5.7-84.4). These differences were statistically significant at log-rank test both for OS and for PFS, *P*<.0001 (Fig. 4).

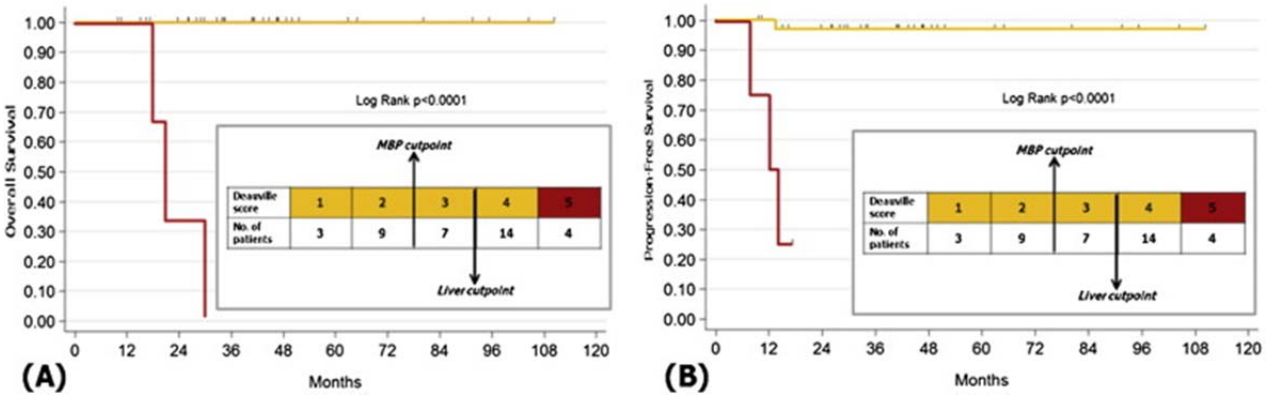

Fig. 4.

Overall (A) and progression-free (B) survival estimates by Deauville score (1-4 vs 5).

Discussion

The aim of this retrospective study was to evaluate the role of RT in PMBCL patients with residual active metabolic disease after R-CT. All analyzed patients were homogeneously treated with a combination of R-CHOP or R-CHOP-like chemotherapy and RT, representing the standard therapeutic approach for all PMBCL patients referred to our department.

The outcome of the whole study population appears well comparable with that reported by other studies testing the combination of R-CHOP/R-CHOP-like chemoimmunotherapy and RT 7, 8 and 9, with 3-year OS and PFS rates of 89.8% and 88.7%.

Several investigators reported on the role of ^{18}FDG-PET in the management of aggressive non-Hodgkin's lymphoma, in particular after completion of first-line therapy, with controversial results 15, 16, 17 and 18. In PMBCL, the role of ^{18}FDG-PET image interpretation is somehow more complex. Most of these patients present at diagnosis with large tumors (bulky disease), and they often have residual disease at CT restaging after chemotherapy (in the present study approximately 80%). The Deauville 5-PS, which was initially proposed as a reporting method for interim ^{18}FDG-PET scans, is very flexible, permitting movement of the positivity threshold across the scores, adapting to the escalating or deescalating intent of different protocols. In the recently opened IELSG37 trial, evaluating the role of consolidative irradiation in ^{18}FDG-PET-negative patients, only scores 1 and 2 were defined as negative (expected rate of 50% of ^{18}FDG-PET-negative patients). Inasmuch as this trial was designed with the aim of avoiding RT in ^{18}FDG-PET-negative patients, this cutoff for ^{18}FDG-PET negativity was considered appropriate and prudential; in ^{18}FDG-PET-positive patients, the indication for further treatment after R-CT is left to the treating physicians, showing the current uncertainty on the appropriate management of these patients. For ^{18}FDG-PET positivity interpretation, the Deauville scoring system has some limitations in correctly discriminating between true refractory disease, minimal residual disease, and inflammatory uptake. The IELSG26 study (19) showed that in PMBCL the rate of positivity at the end of R-CT was higher than reported in DLBCL (scores 3, 4, and 5, 53%; scores 4 and 5, 29.5%); patients with scores 4 and 5 have a worse PFS than do patients with scores 1-3 (even if globally 90% are projected to be alive and free of progression at 5 years). In this study, 9 of 10 relapses and progressions occurred in patients with scores 4 and 5, and the last was in a patient with a score 2 not receiving RT. All patients with score 3 had the same outcome than did patients with scores 1-2. Incorporating these findings in response evaluation would mean that only scores 4 and 5 would be considered positive, and, using this threshold, the results would support the prognostic role of ^{18}FDG-PET positivity after R-CT. This interpretation is partially in contrast with the cutoff chosen for the new IELSG37 study, where patients with a score of 3 are also considered positive.

In the present study, the global clinical outcome was satisfactory, and, similarly to the IELSG26 study preliminary analysis, a significant difference in overall survival was evident when comparing scores 1-3 to scores 4-5, even if unbalanced, as no events occurred in patients with a score of 4 (no specific data are currently available from IELSG26). This is probably one of the most interesting findings, considering that patients with scores 3-5 are frequently regarded as nonresponders and referred to high-dose chemotherapy/autografting. These results thus emphasize the efficacy of RT in controlling disease in the majority of patients with residual metabolic activity after R-CT and confirm the results of other previously published series 5 and 6, based on different functional imaging evaluation at the end of chemotherapy in the era before rituximab. In the study by De Sanctis et al (5), after MACOP-B functional restaging, ^{67}Ga scintigraphy/^{18}FDG-PET was positive in 83% of patients, dropping out to only 21% after RT. A relapse rate of 30.7% was observed in patients with positive findings on ^{67}Ga/^{18}FDG-PET imaging at the end of the program, compared with a relapse rate of 1.8% in patients with negative findings at metabolic restaging. In a series of 50 patients by Zinzani et al (6), treated with MACOP-B and RT, 31 of 47 patients (66%) were ^{67}Ga scintigraphy positive after chemotherapy, compared with 9 of 47 (19%) after RT. The relapse rate was 60% in ^{67}Ga scintigraphy-positive patients at the end of the combined program and 0% in ^{67}Ga scintigraphy-negative patients. In both these series, the percentage of patients with persistent positive findings after chemotherapy was >50%, and RT was able to sterilize residual disease in approximately 75% of patients. On the other side, despite this globally favorable outcome, there is still a subgroup of PMBCL patients with ^{18}FDG-PET positivity after R-CT that cannot be cured with RT, and we therefore hypothesized that the Deauville scoring system would have been able to select those with a poorer prognosis. Our results revealed that patients with a score of 5 are at significantly higher risk of relapse and death in comparison with all other patients, regardless of the addition of full-dose RT after R-CT (radiation dose was not prospectively prescribed on the basis of the Deauville score at the time of treatment, but patients with scores 4-5 received median higher doses, 35.3 Gy, and all patients with score 5 received 36-40 Gy). The limits of our study are mainly represented by its retrospective nature and by the limited number of patients included, with a consequent limited number of events. Moreover, there are still some uncertainties regarding the Deauville visual scoring system, for example in correctly discriminating between score 4, “moderately increased uptake,” and score 5, “markedly increased uptake,” with variations in the distribution of different scores within different cohorts of patients (ie, IELSG26). Consequently, it is not possible to draw any conclusion regarding ^{18}FDG-PET cutoffs, and therefore the results obtained have to be considered as preliminary and should be validated in larger series.

A phase II prospective study testing R-EPOCH regimen in first-line therapy (20) suggests that probably alternative chemotherapy regimens to R-CHOP and R-CHOP-like regimens might substantially improve the response rate and potentially avoid the use of RT. The study included 51 patients prospectively treated with dose-adjusted rituximab-EPOCH for 6 to 8 cycles without RT regardless of the response obtained. Only those with residual masses at CT scan were studied with ^{18}FDG-PET. Of 36 patients in morphologic PR, 18 (50%) had a SUV_{max} at ^{18}FDG-PET < MBP and 18 a SUV_{max} > MBP. In patients with SUV_{max} below the MBP, no events occurred, whereas in the other group, 3 patients experienced recurrence, all of them with a SUV_{max} above 5. These results are interesting for several reasons. First, most ^{18}FDG-PET-positive patients did not experience relapse (the ^{18}FDG-PET positive predictive value seems really lower in PMBCL in comparison with other aggressive B-cell lymphomas). Second, the omission of mediastinal RT in all patients did not affect the global outcome (only 3/51 experienced relapse). Third, higher SUV_{max} values after R-CT in a subgroup of ^{18}FDG-PET-positive patients are associated with a higher risk of relapse, and this last finding nicely supports our hypothesis that we might be able to select patients with a poorer prognosis by quantifying different degrees of metabolic response. If these very encouraging results will be confirmed, it is possible that the use of radiation at the end of R-chemotherapy as well as the early shift to high-dose chemotherapy/autografting will be declining in the next years.

In conclusion, roughly 50% of patients with PMBCL still have residual ^{18}FDG-PET positivity after R-CHOP or R-CHOP-like regimens. The positivity rate is probably the expression of a complex mixture of true residual disease and false-positive findings secondary to inflammation. RT is able to convert in persistent CR approximately 85% of ^{18}FDG-PET-positive patients, producing as a result of the whole therapeutic approach

an expected PFS rate of 85% to 90% at 3 years; patients with very poor metabolic response (Deauville score 5, approximately 10%) appear at higher risk of relapse/progression after RT and should be carefully evaluated for eventual intensification. The role of consolidation RT in ^{18}FDG-PET-negative patients (scores 1-2) will be clarified in the next years by ongoing clinical trials.

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