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Clinical Implications of PET-Negative Residual CT Masses after Chemotherapy for Diffuse Large B-Cell Lymphoma

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Abstract

Response to primary treatment in diffuse large B cell lymphoma (DLBCL) is highly predictive of long-term outcome. We evaluated the value of computed tomography (CT) findings relative to positron emission tomography (PET) findings, after the completion of chemotherapy; we retrospectively reviewed records from 491 patients with DLBCL at MD Anderson in 2001-2007; 22 patients were excluded for uncertain pathology and 169 for having received consolidative radiation, leaving 300 patients for the current analysis (median age, 61 years; 53% men, 47% women; 27% stage I-II, 73% stage III-IV; 73% completed 6-8 cycles of doxorubicin-based therapy). Factors associated with outcome on univariate analysis were response according to PET/CT and CT ($P<0.0001$ for OS, DSS, and PFS); number of chemotherapy cycles received ($P<0.0001$ OS, $P<0.0001$ DSS, $P<0.002$ PFS); the combined presence of Ki-67 $>50\%$, PET SUV 13, and bulky (>5 cm) disease ($P=0.005$ OS, $P=0.001$ DSS, $P=0.001$ PFS); and International Prognostic Index (IPI) score ($P=0.003$ OS, $P=0.005$ DSS, $P=0.003$ PFS). On multivariate analysis, PET/CT-negative, CT residual mass (>2 cm) significantly influenced OS, DSS and PFS ($P<0.0001$). The presence of a residual mass >2 cm on CT, coupled with negative findings on PET/CT, has prognostic value in DLBCL.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive disease constituting 30%-40% of all adult non-Hodgkin lymphomas^{1,2}. Although many patients initially respond to R-CHOP chemotherapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), the 5-year overall survival (OS) rates for patients with DLBCL vary from 45% to 82%,³⁻⁵ reflecting the heterogeneous nature of this disease. The choice of treatment for DLBCL is currently based on pretreatment clinical and cytogenetic features^{6,7,8} that are used to stratify patients into groups with favorable or unfavorable prognosis, and a risk-adapted approach is used to choose the type of chemotherapy and subsequently determine the need for dose intensification. Response to primary treatment in DLBCL is highly predictive of long-term outcome, but the definitions of response have varied widely. Criteria for response assessment have been developed by international working groups in attempts to give clinicians a common language with the goal of reducing heterogeneity when analyzing patient outcomes.⁹ Combining those criteria with use of functional imaging by 18-fluorodeoxyglucose positron emission tomography (FDG-PET) coupled with computed tomography (CT) resulted in the elimination of the CRu category (complete response, unconfirmed)^{9,10} and improved the accuracy of staging and restaging evaluations after primary therapy.¹⁰⁻¹⁴

Although PET/CT is now considered an essential tool to assess response to treatment in lymphoma,¹⁵ its sensitivity and specificity have been the subject of much debate, particularly with regard to issues such as variations among readers and technical aspects of the devices.¹⁵ In current clinical practice, CT is still considered an important adjunct to PET for diagnosis, and in some practices patients will continue to have diagnostic contrast-enhanced CT scans to confirm remission status after therapy.

We undertook this study to evaluate the potential value of the CT findings relative to PET findings, both obtained after the completion of chemotherapy, for patients with DLBCL with regard to OS and progression-free survival (PFS). We specifically wanted to evaluate if a residual mass on CT in the presence of negative findings on PET is of any prognostic significance. All patients in this study received chemotherapy only; no patient received radiation.

Patients and Methods

The appropriate institutional review board of The University of Texas MD Anderson Cancer Center approved this study. We retrospectively reviewed the records of 491 patients who had been referred to MD Anderson Cancer Center for treatment of DLBCL in 2001-2007. Twenty-two patients were excluded from the analysis because pathologic findings could not be confirmed or treatment was not given at MD Anderson. Another 169 patients were excluded because they had received radiation therapy after chemotherapy. Those patients were excluded in an effort to eliminate bias from the known effectiveness of radiation in converting partial or unconfirmed remissions into complete remissions (CR) and because the choice of whether to use radiation or not was not made consistently throughout the study period. Our previous analysis of this population showed that radiation given after chemotherapy had a significant effect on OS and PFS for patients who achieved CR after chemotherapy.¹⁶ Thus our study group consisted of 300 patients who had received chemotherapy alone for pathologically confirmed DLBCL. Pretreatment variables extracted from the records included age, sex, Ann Arbor clinical disease stage,¹⁷ the presence or absence of bulky disease (defined at our institution as mass >5 cm in diameter), International Prognostic Index (IPI) score, Ki-67 immunostaining¹⁸ (a marker of tumor proliferation rate assessed in pathology specimens), and PET standardized uptake values (SUVs). We also

extracted data on disease status at the completion of chemotherapy, based on PET/CT fusion scans (all obtained on Discovery hybrid PET/CT systems [GE Healthcare]) and contrast-enhanced CT scans, date of last follow-up, and patient status at last follow-up. PET/CT was performed 3 to 4 weeks after completion of chemotherapy. In an attempt to minimize variability between readers, all SUV_{max} measurements were obtained with a volume viewer tool that calculates the SUV_{max} in a volume of interest defined by the user. All SUV measurements were based on whole body mass. Two nuclear medicine physicians read all scans, and discordance was resolved by a third. Ki-67 values were grouped as < 50% or 50%. Diagnostic PET SUVs were grouped as ≤ 13 or >13 extrapolating from a 2009 report that an SUV >13 separates indolent from aggressive/diffuse large cell lymphoma histologies in non-Hodgkin's lymphoma with greater than 90% certainty and also based on our previously published data.¹⁹ The term “PET” is used hereafter to refer to FDG activity from PET/CT fusion scans.

Results

Clinical Characteristics

Clinical characteristics of the 300 patients with histologically confirmed DLBCL are summarized in Table 1. The median age at diagnosis was 61 years (range, 20-89 years). Slightly more patients were male, and most had Ann Arbor clinical stage IV disease at diagnosis. Bulky disease (>5 cm) was present in 121 patients (40.3%). SUV values were ≤ 13 for 179 patients and >13 for 121. Proliferation rate, measured by Ki-67 immunostaining, was 50% in 153 (74%) of the 207 patients for whom this information was available. The median follow-up interval was 61 months (range, 5-118 months). Twenty-nine of the 207 patients (10%) for whom information on bulky disease, SUV, and Ki-67 was available had triple-positive disease (bulky disease, SUV >13, and Ki-67 ≥ 50%), and 28 (11%) had triple-negative disease (no bulky disease, SUV ≤ 13, and Ki-67 <50%) after chemotherapy. Most patients (60%) had an IPI score of 1 or 2.

Treatment

Most patients (285 of 300) received doxorubicin-based therapy. Two hundred forty-four (73%) patients received R-CHOP [cyclophosphamide 750 mg/m²; doxorubicin 50 mg/m²; vincristine 1.4 mg/m² (for a maximum single dose of 2 mg) given intravenously on day 1; along with 100 mg oral prednisone on days 1–5] given every 21 days; 218 patients received 6-8 cycles and the other 26 (9%) received fewer than 6 cycles. An additional 41 patients (14%) received R-Hyper-CVAD [rituximab 375 mg/m²; cyclophosphamide 300 mg/m² intravenously (IV) over 3 hours every 12 hours for six doses on days 1 through 3, with mesna at the same total dose as cyclophosphamide but given by continuous infusion starting with cyclophosphamide and ending 6 hours after the last dose; vincristine 2 mg IV days 4 and 11; doxorubicin 50 mg/m² IV day 4; and dexamethasone 40 mg daily on days 1 through 4 and 11 through 14], and 15 (5%) patients received other chemotherapy regimens. A total of 246 patients (82%) had 6-8 cycles of doxorubicin-based regimens, 47 (15%) had fewer than 6 cycles, and 7 patients (3%) had non-doxorubicin-based chemotherapy. Variations in treatment approach, including type of chemotherapy and number of cycles, were at the discretion of the medical oncologist.

Response

CR by both PET/CT and CT was achieved in 155 patients (52%); CR by the PET component of PET/CT but PR by CT was achieved in 93 patients (31%); and PR by both PET components of PET/CT and CT in 52 patients (17%). Of the 93 patients with negative PET component of PET/CT who showed evidence of residual disease after chemotherapy on CT, 62 had residual lesions ≤ 2 cm, 26 had lesions between 2 and 5 cm, and 4 had lesions >5

cm, and one had no residual disease. In terms of number of residual sites, 50 patients had 1 residual site, 32 had 2-3 residual sites, and 10 had > 3 residual sites.

Univariate Survival Analyses

Findings from univariate analyses of all 300 patients and of 248 patients (excluding 52 patients with progressive disease) are shown in Tables 2 and 3. Factors found to be associated with OS, DSS, and PFS were type and number of cycles of chemotherapy; IPI score; the presence or absence of the three adverse factors (triple-negative vs. triple-positive); and response to chemotherapy (represented by disease status on both PET and CT as well as number and size of residual sites). With regard to chemotherapy, the 5-year OS, DSS and PFS rates for those treated with 6-8 cycles of R-CHOP chemotherapy were 77%, 80% and 75%, respectively, and the corresponding rates for those treated with <6 cycles of R-CHOP were 48% OS ($P<0.0001$), 51% DSS ($P<0.0001$), and 46% PFS ($P<0.002$). The 5-year OS, DSS, and PFS rates for those who did not receive doxorubicin-based chemotherapy were 33%, 39%, and 50%. Patients who presented with an IPI score of 0 had 5-year OS, DSS and PFS rates of 90%, 93%, and 93%, respectively; these rates were lower for patients who presented with an IPI score of 1-2 (71% OS, 75% DSS, and, 71% PFS) or an IPI score of 3 (58% OS, $P=0.003$; 62% DSS, $P=0.005$, and 60% PFS, $P=0.004$) (Figure S1).

In considering the composite score (the combination of the adverse factors SUV, Ki-67, and bulky disease), we found that patients who presented with none of these risk factors (triple-negative, i.e., SUV <13, Ki-67 <50%, and non-bulky tumors) had significantly higher OS (92%), DSS (100%), and PFS rates (96%) than did patients with all three risk factors (triple-positive; OS 51%, $P=0.005$; DSS 54%, $P=0.001$; and PFS 51%, $P=0.001$). None of these risk factors, when considered separately, were significant except for bulky disease on OS ($P=0.031$) and DSS ($P=0.035$) and Ki-67 expression on PFS ($P=0.036$) (Table 2).

In terms of response, the 5-year OS, DSS, and PFS rates for patients who achieved CR by both PET and CT were significantly higher (85% OS; 87% DSS; 84% PFS) than the rates for those who achieved CR by PET only (66% OS; 71% DSS; 64% PFS) or for those who did not achieve a CR (i.e., with residual disease) on both PET and CT (35% OS, $P<0.0001$; 40% DSS, $P<0.0001$; and 42% PFS, $P<0.0001$). The number of residual disease sites was associated with 5-year OS, DSS and PFS as follows: 1 site, 89% OS, 90% DSS, and 84% PFS; 2-3 sites, 46% OS, 52% DSS, and 48% PFS; and >3 sites, 17% OS ($P<0.001$), 24% DSS, and 25% PFS ($P<0.001$). In terms of the size of the residual mass (detected by CT), OS, DSS and PFS were significantly better for patients with no residual disease (84% OS, 86% DSS, and 84% PFS) than for those with <2-cm residual (72% OS, 74% DSS, and 70% PFS) or those with ≥2-cm residual (32% OS, 40% DSS, and 40% PFS, all $P<0.0001$).

Little difference was noted in these findings when the analyses were restricted to the 248 patients who had CR on PET (i.e., not including the 52 patients with progressive disease) (Table S1). Again, the most significant factors were IPI score ($P=0.014$ OS, 0.017 DSS, and 0.015 PFS), composite risk factors ($P=0.007$, 0.0003, and 0.0006), and response to therapy including the presence or absence of mass on CT ($P=0.002$, 0.006, and 0.001), number of residual sites ($P<0.0001$ for all), and size of the residual site ($P<0.0001$ for OS, DSS, and PFS). Survival curves according to response on imaging, number of residual sites, and size of residual sites are shown in Figure 1

Multivariate Survival Analyses

We also ran multivariate analyses first with all 300 patients and then with the 248 patients who did not have progressive disease. We further tested 3 different Cox regression models that varied as to whether they included response according to (1) the status of disease on

PET and CT or (2) the number of residual sites or (3) the size of residual sites (Table 4 and S2-S4), OS, DSS, and PFS were found to be significantly influenced by type and number of cycles of chemotherapy, with the best outcome for patients receiving 6 cycles of R-CHOP; IPI score, the best being a score of 0-1; and disease status by PET and CT at completion of therapy, the best being a CR by both PET and CT.

We also did a multivariate analysis of the 248 patients (excluding the 52 patients with progressive disease), all of who would be considered in remission at the completion of chemotherapy except for CT status (Tables S5-S7). We used the same three models to assess the influence of disease status after chemotherapy. Disease stage was significant for OS, DSS, and PFS, IPI score was significant only for OS; and composite score was significant for DSS and PFS.

We further performed another multivariate analysis comparing patients given 6-8 cycles of any doxorubicin-based chemotherapy versus those who did not (as opposed to patients who received 6-8 cycles of R-CHOP vs. those who did not), and we found that the same factors remained significant (not shown).

Failure Patterns

The patterns of treatment failure were consistent with the predictions of the univariate and multivariate analyses with regard to disease status on PET/CT after chemotherapy. Of the 248 patients without progressive disease, 51 (20%) experienced failure on follow-up scans: 23 failures (15%) appeared in the 155 patients achieving CR by both PET and CT compared with 28 failures (30%) in the 93 patients achieving CR by PET but with residual disease on CT ($P=0.004$). Finally, with regard to size of the residual mass on CT and patterns of failure, 24 of the 155 patients (15%) with no residual disease experienced failure, 14 of 62 (23%) with residual disease ≤ 2 cm, and 13 of 30 (43%) with disease >2 cm experienced failure ($P=0.002$). Patients experiencing failure went on to receive salvage chemotherapy at standard or high doses according to institutional guidelines.

Discussion

Currently, PET in combination with CT is increasingly used for assessment of tumor response after therapy. Recent studies have established the high sensitivity and specificity of PET scan for predicting disease relapse (50%-100% sensitivity and 67-100% specificity).²⁰⁻²² The resolution of PET activity after treatment is an essential part of the current definition of CR put forth by the International Harmonization Project,²³ which was created to address the need to improve consistency of reporting. Other such efforts include use of the 5-point Deauville criteria for evaluating PET analyses.^{24,25} The role of interim PET/CT has been also established with emerging data that integrated PET/CT PET/CT scanning as a useful tool for assessing mid-therapy response and possibly tailoring the therapy accordingly.^{26,27} Therefore, we believed that looking at the possible contribution of CT in the setting of negative FDG-avid disease is worth doing to further clarify the definition of response to therapy. We found that the presence of a residual mass on CT in patients with a negative PET scan at the completion of chemotherapy for DLBCL may be important in predicting inferior OS and PFS. We further found that OS, DSS, and PFS were significantly poorer when the residual mass or masses visualized on CT were larger than 2 cm, despite negative findings on PET. Our results were statistically significant in both univariate and multivariate analyses and consistently kept their significance even when different groupings of patients were used and when different variables were considered in the statistical model. Notably, none of the patients in these analyses had received radiation for consolidation therapy, which allows us to assess the extended prognosis of these patients.

according to their response to chemotherapy alone, without the possible added therapeutic benefit of radiation therapy.

Response to primary therapy for DLBCL is highly predictive of long-term outcome.²⁸ The prognosis for patients achieving less than a CR or for those who experience recurrence after primary therapy is often dismal, with fewer than 30% surviving for 5 years.²⁹ Thus further refinements to diagnostic tools and better understanding of the implications of diagnosis with respect to outcome are still crucial. The importance of >2-cm residual disease on CT is recognized in patients with advanced Hodgkin's lymphoma, as evidenced by many ongoing trials introducing radiation for PET-positive and residual mass of ≥ 2.5 cm on CT, such as that of the German Hodgkin Study Group. On the other hand, published results from that study suggest that simply observing patients with PET-negative disease and ≥ 2.5 -cm masses on CT, rather than subjecting them to biopsy or irradiation, does not seem to affect outcome.³⁰

Since the introduction of PET scanning in clinical settings, several studies have addressed its use in lymphoma. Our findings agree with published reports of PET sensitivity and specificity from 50% to 100%¹⁵ and confirm that there is room for improvement in the predictive value of the imaging studies. One such improvement would be considering the presence of residual masses on CT in addition to PET findings after therapy.

Our findings confirmed several known prognostic factors for patients with DLBCL, including response to therapy, type of therapy, IPI score, and triple-positive status, the last of which incorporates factors thought to correlate with the proliferative index of the disease. One implication of our findings is that any residual disease larger than 2 cm on CT after therapy should be regarded with suspicion, and such masses should be either subjected to biopsy or followed closely over time for evidence of treatment failure. If residual disease is present at more than one site, the index of suspicion for aggressive disease should be even higher. Another implication of this study is that radiation therapy may be particularly useful for patients in whom residual masses are present; we showed previously that consolidation radiation therapy was beneficial in multivariate analysis for both OS (hazard ratio=0.19, $P<0.0001$) and PFS (hazard ratio=0.32, $P<0.0001$) for patients with disease at any stage but especially for those with early-stage disease.¹⁶

Our study does have several shortcomings, foremost among them being its retrospective nature and the subjectivity associated with reading PET scans. As is true for most studies that span a 7-year period, PET scanning procedures were not uniform and different radiologists read the PET scans. Using SUVmax of 2.5 might not be ideal for small lesion because of respiratory motion and partial volume effects, therefore visual assessment becomes more accurate and that can introduce reader dependent variation. We attempted to reduce this variability by considering only negative PET scans and by having two nuclear medicine radiologists read all of the PET scans and all of the CT scans showing evidence of residual masses and reach consensus on the PET scan as well as the size of the mass. We further attempted to reduce bias caused by the ability of radiation therapy to convert possible PRs into CRs by excluding otherwise eligible patients who had had radiation therapy after chemotherapy, which reduced our patient numbers from 469 to 300. Another shortcoming, by lumping bulky disease, SUV and Ki67 into one we ended up with only 10 % of the patients, those who had data to allow this distinction, which potentially can make our conclusions less solid and open to question, and finally this needs to be validated by other groups.

There is no doubt that FDG-PET/CT has become an effective tool for assessing response to therapy, but we believe the CT component still has value. We conclude that the presence of

a residual mass on CT after chemotherapy has both prognostic and predictive value for patients with DLBCL. In particular, biopsy and consolidative therapy should be considered for patients with one or more residual masses, or any mass larger than 2 cm in diameter. We hope that other groups will validate our findings, preferably in prospective trials. If these findings are confirmed, we suggest that they be incorporated into new treatment guidelines for patients with DLBCL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Overall survival, disease specific survival, and progression-free survival according to (A) type of response (CR by PET/CR by CT vs. CR by PET/CTvs. PR by CT), number of residual disease sites (0, 1, 2, or 3), and size of residual disease sites (0 cm, <2 cm, >2 cm) in 248 patients with PET-negative disease after chemotherapy.

Table 1

Patient Characteristics

Characteristic	All Patients No. (%) (n=300)	CR by Both PET and CT No. (%) N=155	CR by PET Only No. (%) N=93	PR by Both PET and CT No. (%) N=52	P Value
Sex				0.496	
Female	142 (47.3)	74 (47.7)	47 (50.5)	21 (40.4)	
Male	158 (52.7)	81 (52.3)	46 (49.5)	31 (59.6)	
Disease stage					0.009
I	36 (12.0)	22 (14.2)	9 (9.7)	5 (9.6)	
II	45 (15.0)	24 (15.5)	12 (12.9)	9 (17.3)	
III	60 (20.0)	24 (15.5)	31 (33.3)	5 (9.6)	
IV	159 (53.0)	85 (54.8)	41 (44.1)	33 (63.5)	
Chemotherapy					0.204
R-CHOP < 6	26 (8.7)	11 (7.1)	7 (7.5)	8 (15.4)	
R-CHOP 6	218 (72.7)	120 (77.4)	68 (73.1)	30 (57.7)	
R-HCVAD	41 (13.7)	17 (11.0)	13 (14.0)	11 (21.2)	
Others	15 (5.0)	7 (4.5)	5 (5.4)	3 (5.8)	
Bulky disease					0.070
5 cm	177 (59.0)	101 (65.6)	50 (54.3)	26 (50.0)	
> 5 cm	121 (40.3)	53 (34.4)	42 (45.7)	26 (50.0)	
Missing	2 (0.7)				
PET SUVs					0.009
13	179 (59.7)	105 (68.6)	46 (50.0)	28 (53.8)	
> 13	118 (39.3)	48 (31.4)	46 (50.0)	28 (46.2)	
Missing	3 (1.0)				
Ki-67 expression					0.165
< 50%	54 (18.0)	33 (30.8)	12 (17.9)	9 (27.3)	
50%	153 (51.0)	74 (69.2)	55 (82.1)	24 (72.7)	
Missing	93 (31.0)				
Composite score					0.005
0 risk factor	28 (9.3)	21 (19.6)	7 (10.4)	0	
1-2 risk factors	150 (50.0)	78 (72.9)	46 (68.7)	26 (78.8)	

Characteristic	All Patients No. (%) (n=300)	CR by Both PET and CT No. (%) N=155	CR by PET Only No. (%) N=93	PR by Both PET and CT No. (%) N=52	P Value
3 risk factors	29 (9.7)	8 (7.5)	14 (20.9)	7 (21.2)	
Missing	93 (31.0)				
International Prognostic Index Score					0.093
0-1	37 (12.3)	21 (13.5)	13 (14.0)	3 (5.8)	
1-2	181 (60.3)	99 (63.9)	47 (50.5)	35 (67.3)	
3	82 (27.3)	35 (22.6)	33 (35.5)	14 (26.9)	
Size of residual sites					<.0001
No residual	156 (52.0)	155 (100.0)	1 (1.1)	0	
< 2 cm	86 (28.7)	0	62 (66.7)	24 (46.1)	
2 cm	58 (19.3)	0	30 (32.2)	28 (53.9)	
Number of residual sites					<.0001
0	156 (52.0)	155 (100.0)	1 (1.1)	0	
1 site	57 (19.0)	0	50 (53.8)	7 (13.5)	
2-3 sites	56 (18.7)	0	32 (34.4)	24 (46.1)	
> 3 sites	31 (10.3)	0	10 (10.7)	21 (40.4)	

Abbreviations: CR, complete response; PR, partial response; PET, positron emission tomography; CT, computed tomography; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SUV, standardized uptake value. Triple negative is defined as no bulky disease, SUV ≤ 13 , and Ki-67 $\leq 50\%$; triple positive as bulky disease, SUV > 13 , and Ki-67 $> 50\%$.

Table 2
Univariate Analysis of Overall, Disease-Specific, and Progression-Free Survival for all 300 Patients

Variable	5-year OS (95% CI)	P Value	5-year DSS (95% CI)	P Value	5-year PFS (95% CI)	P Value
Age, years		0.231		0.445		0.965
60	71.8 (63.0-78.8)		75.6 (66.9-82.4)		70.5 (61.5-77.7)	
>60	68.0 (59.4-75.2)		71.8 (63.0-78.8)		70.9 (62.3-77.9)	
Disease stage		0.295		0.157		0.027
I-II	78.6 (67.0-86.5)		80.0 (68.1-87.9)		82.5 (71.2-89.7)	
III-IV	66.6 (59.4-72.8)		71.4 (64.1-77.4)		66.3 (59.0-72.6)	
Chemotherapy		<0.0001		<0.0001		0.002
R-CHOP < 6	47.8 (26.8-66.1)		51.2 (28.4-70.1)		45.5 (24.4-64.3)	
R-CHOP ≥ 6	76.6 (69.8-82.1)		79.7 (73.0-84.9)		75.3 (68.3-80.9)	
R-HCVAD	63.2 (45.9-76.3)		67.7 (49.2-80.6)		69.9 (52.2-82.0)	
Others	33.3 (11.3-57.5)		39.1 (13.2-64.7)		50.0 (20.9-73.6)	
Bulky disease		0.031		0.035		0.062
5 cm	75.3 (67.4-81.5)		79.0 (71.2-84.9)		75.4 (67.5-81.7)	
>5 cm	63.1 (53.4-71.3)		67.0 (57.0-75.2)		64.8 (55.0-73.0)	
PET SUV		0.826		0.805		0.576
13	71.1 (63.4-77.4)		74.3 (66.5-80.5)		73.4 (65.8-79.6)	
>13	66.8 (56.3-75.4)		71.9 (61.3-80.1)		65.2 (54.6-74.0)	
Ki-67 staining		0.339		0.063		0.036
<50%	77.1 (62.5-86.6)		88.5 (74.6-95.1)		86.7 (72.7-93.8)	
50%	71.9 (78.8)		72.8 (64.0-79.9)		68.6 (59.8-75.9)	
Composite score		0.005		0.001		0.001
0 risk factor	91.8 (71.1-97.9)		100.0		95.7 (73.4-99.4)	
1-2 risk factors	74.0 (65.5-80.8)		77.2 (68.6-83.8)		73.5 (64.8-80.4)	
3 risk factors	51.0 (30.2-68.5)		54.2 (32.7-71.4)		51.0 (30.2-68.5)	
International Prognostic Index Score		0.003		0.004		0.004
0-1	90.3 (72.9-96.8)		93.3 (75.9-98.3)		93.4 (76.2-98.3)	
1-2	71.1 (63.2-77.5)		74.7 (66.9-81.0)		71.1 (63.1-77.6)	
3	58.3 (46.1-68.7)		62.4 (49.6-72.8)		60.0 (47.6-70.4)	
Response		<0.0001		<0.0001		<0.0001

Variable	5-year OS (95% CI)	P Value	5-year DSS (95% CI)	P Value	5-year PFS (95% CI)	P Value
CR PET + CR CT	84.5 (77.2-89.6)		86.7 (79.5-91.5)		84.2 (76.8-89.4)	
CR PET + PR CT	65.6 (53.7-75.1)		70.6 (58.6-79.8)		63.8 (51.8-73.5)	
PR PET + PR CT	34.7 (21.7-48.1)		40.2 (25.8-54.2)		42.2 (27.8-56.0)	
Number of residual sites		<0.0001		<0.0001		<0.0001
0	83.9 (76.6-89.1)		86.1 (78.9-91.0)		83.6 (76.2-88.9)	
1 site	88.5 (74.6-95.1)		90.4 (76.3-96.3)		84.1 (69.5-92.1)	
2-3 sites	45.5 (31.3-58.5)		51.6 (36.7-64.6)		47.9 (33.3-91.1)	
>3 sites	17.2 (6.3-32.7)		24.0 (9.8-41.7)		24.5 (10.4-41.7)	
Size of residual sites		<0.0001		<0.0001		<0.0001
No residual	83.9 (76.6-89.1)		86.1 (78.9-91.0)		83.6 (76.2-88.9)	
<2 cm	72.1 (59.8-81.2)		74.1 (61.6-83.0)		67.9 (44.4-77.5)	
2 cm	31.5 (19.7-43.9)		40.2 (26.5-53.5)		40.0 (26.5-53.1)	

Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidence interval; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; PET, positron emission tomography; CT, computed tomography; CR, complete response; PR, partial response. Triple negative is defined as no bulky disease, SUV ≥ 13 , and Ki-67 $\geq 50\%$.