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R-CHOP 14 with or without radiotherapy in non-bulky limited-stage diffuse large B-cell lymphoma (DLBCL)

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ABSTRACT

The benefit of radiotherapy (RT) following chemotherapy in limited-stage diffuse large B-cell lymphoma (DLBCL) remains controversial. Before the Rituximab (R) era, randomized trials have reported conflicting results. We conducted a randomized trial in patients with non-bulky (tumor size <7cm) limited-stage DLBCL to evaluate the benefit of RT following R-CHOP.

Patients were stratified according to the Miller modified IPI (mIPI) including LDH (normal/elevated), ECOG performance status (0-1/2-3), age (<60/>60 yrs) and disease stage (I/II). The patients received 4 or 6 consecutive cycles of R-CHOP delivered every two weeks, followed or not by RT at 40 Gy delivered 4 weeks after the last R-CHOP cycle. All patients were evaluated by FDG-PETs performed at baseline, after 4 R-CHOP cycles and at the end of treatment. The primary objective of the trial was event-free survival (EFS) from randomization.

The trial randomized 165 patients in the R-CHOP arm and 169 in the R-CHOP+RT arm. In an intent to treat analysis, with a median follow-up of 64 months, five-year EFS was not statistically different between the two arms, with 89% \pm 2.9 in the R-CHOP arm vs 92% \pm 2.4 in the R-CHOP+RT arm (HR 0.61, 95%CI 0.3 to 1.2, p=0.18). Overall survival was also not different at 92% (95% CI: 89.5-94.5) for patients assigned to R-CHOP alone, and 96% (95% CI: 94.3-97.7) for those assigned to R-CHOP+RT, (p=ns)

R-CHOP alone is not inferior to R-CHOP followed by RT in patients with non-bulky limited-stage DLBCL. (ClinicalTrials.gov number, NCT00841945).

INTRODUCTION

Combined modality therapy based on abbreviated chemotherapy followed by radiotherapy (RT) has been considered until recently as the standard-of-care of early-stage diffuse large B-cell lymphoma (DLBCL).^{1,2} In the context of limited stage DLBCL, this option has been challenged by using chemotherapy or, nowadays, immuno-chemotherapy (R-CHOP) alone.³ In 2010, the National Comprehensive Cancer Network (NCCN) guidelines recommended three cycles of R-CHOP followed by involved field radiotherapy (IF-RT) for early-stage, non-bulky DLBCL, as well as the administration of six to eight cycles of R-CHOP with or without IF-RT.⁴ To date, no definitive conclusions can be drawn for the need of consolidative IF-RT for patients with early-stage DLBCL.

Before the rituximab era, four randomized trials raised the question of adding RT after chemotherapy in order to provide a more effective local control and hopefully an advantage in terms of disease-free survival.⁵⁻⁸ These results have been widely commented over the last decade, leading to conflicting conclusions depending on the various chemotherapy options of these trials (3, 4 or 8 CHOP courses or AVCBP high-dose therapy regimen), patient selection and time of analysis.⁹

Whether or not RT should be added to R-CHOP in limited-stage DLBCL is also controversial.¹⁰⁻¹⁴ In a large retrospective study, it was shown recently that only 39% of patients with early-stage DLBCL were delivered RT in the USA.¹¹ However, no prospective trials have been published so far in this setting in the rituximab era. It has been raised by Ng et al. that we definitely need randomized trials using contemporary R-CHOP and PET imaging to select patients for an optimized therapy.¹⁵

Moreover, response to treatment is now based on positron emission tomography (PET) imaging. The British Columbia Cancer Agency has suggested that patients who reach partial response after R-CHOP defined on PET-imaging could optimally benefit from RT, suggesting that patients in complete response (CR) after 3 or 4 cycles of R-CHOP could be spared additional RT.¹⁶⁻¹⁷

In 2005, The LYSA/GOELAMS group initiated a randomized study comparing R-CHOP alone to R-CHOP and RT in patients with early-stage DLBCL and no bulky disease, the results of which are reported here.

PATIENTS AND METHODS

Patients

Patients eligible for enrollment had to be between 18 and 75 years old, with a previously untreated DLBCL according to the 2001 World Health Organization (WHO) classification.¹⁸ Patients were required to have an Ann Arbor stage I or II limited lymphoma, with non-bulky mass defined by a tumor less than 7 cm in diameter. In fact, even in 2017, definition of bulky disease remains arbitrary and varies between 5 and 10 cm depending on the studies and the cooperative groups.^{14, 19-20}

Exclusion criteria were i) positive serology for HIV or active chronic hepatitis B or C, ii) transformation of a previously indolent lymphoma, iii) primary cerebral lymphoma, iv) previous organ transplantation, v) concomitant or previous cancer (except in situ cervical carcinoma), vi) liver or kidney failure and vii) cardiac contraindication to doxorubicin. Patients with cutaneous, testis, ovarian, breast or intestinal lymphoma were also excluded.

The study was conducted according to the principles of the Declaration of Helsinki and the International Conference of Harmonization Guidelines for Good Clinical Practice. The trial was approved by the ethics committee of Rennes University Hospital and all patients provided written informed consent. This trial was registered as ClinicalTrials.gov #NCT00841945.

Pathology

Histological diagnosis was performed by local hemopathologists. Central review was conducted by an expert LYSA/GOELAMS pathologist allowing to reclassify tumors according to the WHO 2008 classification for the final analysis.²¹ Tissue microarrays (TMAs) were constructed using all available

samples and stained for CD20, CD5, CD10, BCL2, BCL6, MYC and MUM1 in immunohistochemistry (IHC). Cell of origin identification was based on Hans' algorithm.

Staging

The extent of the disease was evaluated by physical examination, computed tomography (CT-SCAN) of head, neck, chest, abdomen and pelvis, cerebrospinal fluid examination, bone marrow biopsy and other investigational procedures depending on clinical symptoms. The lymphoma stage was defined as per Ann Arbor Staging System (stage I: involvement of a single lymph-node or extranodal site; stage II: involvement of two or more nodal regions or of an extranodal site and one or more adjacent nodal regions on the same side of the diaphragm.) Tumor measurements were obtained before biopsy, and bulky disease was defined as more than 7 cm in diameter measured in both transverse and coronal planes. Performance status (PS) was assessed at baseline according to the Eastern Cooperative Oncology Group (ECOG) scale. A stage-modified version of the International Prognostic Index (mIPI) was used, considering adverse risk factors for early stage as follows: elevated serum lactate dehydrogenase (LDH) levels, age over 60 years-old, Ann Arbor Stage II, PS ≥ 1 .³

PET assessment at inclusion was mandatory and reviewed by two independent nuclear physicians, in real time. Patients with stage I or II according to CT-scan were excluded if PET assessment disclosed a more extensive lymphoma dissemination upstaging to stage III or IV. PET positivity was defined visually as ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) uptake above mediastinum or surrounding background in a location incompatible with normal anatomy or physiology.²² A negative scan was defined as having no abnormally increased ¹⁸F-FDG at any site.

Treatment

Patients were randomized upfront to receive or not RT after 4 or 6 cycles of R-CHOP (doxorubicin 50 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg /m² [up to a maximal dose of 2 mg] on day 1 and 40 mg/m² prednisone on days 1 through 5) combined with rituximab (375 mg/m² on day 1)

repeated at 14-day intervals. Patients without any adverse prognostic factor (normal LDH level, Ann Arbor stage-I, PS=0, and less than 60 years old, IPI modified =0) received 4 R-CHOP cycles, whereas those with one or more adverse prognostic factors (high LDH level, Ann Arbor stage II, PS over 0, age over 60 years old, modified IPI ≥ 1) received 6 R-CHOP cycles. IF-RT began one month after the last cycle of R-CHOP in the group of patients initially randomized to receive radiotherapy. The prescribed dose of radiation was 40 Gy in 20 fractions of 2 Gy, five days per week. Irradiated volumes encompassed involved nodal or extranodal sites and adjacent uninvolved nodes according to involved field radiotherapy (IFRT). The design of the study is depicted in supplemental data, (Supplemental figure 1). Complete responders pursued treatment according to randomization. Partial responders after the fourth R-CHOP cycle were recommended to receive 2 additional cycles followed by RT whatever the allocated arm. Patients with progressive disease were withdrawn from the study.

Response assessment

Response was evaluated two weeks after the fourth course of R-CHOP, based on PET and CT-scan results, blinded by arm assignment, and four weeks after the end of treatment. (Response criteria in supplemental appendix)

Statistical analysis

Randomization was centralized and stratified according to mIPI. The primary objective of the trial was event-free survival (EFS) from randomization. Secondary end points were overall survival (OS) and toxicity. Based on a non-inferiority analysis, with an upper limit of 10% difference between the two arms in terms of EFS, an 80% power and a bilateral type 1 error of 5%, 170 patients were required for each arm. Due to a lower recruitment than expected, this study was extended to June 2014. An interim analysis performed in 2011 after the inclusion of 270 patients showed estimated OS and EFS at 96% and 94%, respectively and allowed to decrease the upper limit to 8% difference. Analyses were performed by intention to treat. Response and progression under therapy were analyzed by use

of Fisher's exact test. Event-free survival was calculated from the date of randomization to the date of first appearance of disease progression, relapse or death from any cause. Patients alive without progression or relapse were censored at the date they were last known to be alive.

EFS and OS were estimated according to Kaplan-Meier, and the differences between groups compared by use of log-rank test. Differences between groups were calculated on the basis of rounded estimates, whereas 95% CI for these differences were calculated on the basis of exact estimates. Kaplan-Meier estimates at 5 years, with 95% CI, were calculated for the probability of not having an event in the endpoints of EFS, and OS.

RESULTS

Patients

Between May 2005 and June 2014, 334 patients were enrolled at 42 participating French institutions, 165 being randomly assigned to R-CHOP alone and 169 to R-CHOP followed by RT (Figure 1). Fifteen patients were excluded for misdiagnosis (n=4), protocol violation (n=1), consent withdrawal (n= 1), lost to follow-up (n=8), progressive solid tumor one month after randomization (n=1). The main characteristics of the patients were similar in the two groups (Table 1). Most of them (315/334, 94%) had a very favorable mIPI (score 0 or I). About one third of the whole cohort (121/334, 36%) was over 60 years of age and therefore allocated to receive 6 R-CHOP cycles. Extra-nodal involvement accounted for 39% of the whole cohort. The main localizations were Waldeyer ring and tonsils (n=34), cavum and sinus (n=23), mediastinum (n=21), tongue (n=11), bone (n=10), parotid (n=10), thyroid (n=6) and other sites (n=12). Sixty-two patients had a negative PET at baseline following complete resection of the tumor after initial surgery, yet were well-balanced between the two groups. CR patients with a mIPI at 0 were allocated to receive only 4 R-CHOP cycles (n=187) while those with one

or more adverse prognostic factors (n=148) were allocated to receive 2 additional R-CHOP cycles. We confirm that germinal center (GC) subtype was predominantly observed in limited stage DLBCL as compared to activated-B-cell phenotype, in 57% vs 27%, respectively.²³

Response to treatment (table 2)

An interim analysis was performed after the fourth cycle of R-CHOP based on clinical examination, CT-scan and PET. CR was observed in 281 patients (88%) and PR in 38 (12%), without any difference between the two arms. PET was omitted in 4 patients considered to be in PR whatever the CT scan result. R-CHOP cycles 5 and 6 were delivered to 123 and 118 patients respectively (61/57 in the R-CHOP arm and 62/61 in the R-CHOP+RT arm). Two patients did not receive cycles 5 and 6 by medical decision and 5 did not receive cycle 6 due to toxicity (one toxic death during febrile neutropenia and 4 grade 4 hematological toxicity after cycle 5). According to initial randomization, among the 281 patients in CR following R-CHOP, 144 received RT and 137 did not receive any further treatment. Eight patients declined RT for personal reasons.

Treatment of the 38 PR after 4 cycles of R-CHOP included: 2 additional R-CHOP cycles and RT in 27 cases, 2 additional R-CHOP cycles without RT (n=5), high dose chemotherapy (n=3), no further treatment (n=3). CR was documented in 28 cases and the 10 remaining patients were still considered in PR. Two patients with positive PET at the end of treatment are alive and have been disease-free for more than 4 years following the end of therapy. (Supplemental figure 2).

Dose delivery and toxicity

The median relative dose-intensity of cytotoxic drugs (adriamycin and cyclophosphamide) was 97% (97–98) of the planned schedule. Intervals between each cycle of R-CHOP were maintained from cycle 1 to cycle 4 and cycle 5 to cycle 6 with a median of 14 days. The 4 days median of delay

between cycles 4 and 5 was mainly due to the time needed for response assessment by PET. The median time between the last R-CHOP course and day 1 of radiotherapy was 36 days (10-132). During R-CHOP administration, hematological toxicity was rare, with 66 episodes of febrile neutropenia occurring in 50 patients during chemotherapy. There were 4 severe infections and one death due to septic shock. Red blood-cell transfusions were needed for 18 patients (6%). There was no grade 4 thrombocytopenia. After radiotherapy, two patients presented with grade 3 mucositis and jaw radionecrosis was observed in one case. Severe and moderate cardiac toxicity were observed in 5 and 8 cases respectively, regardless the arm of treatment. They were 4 cases of cardiomyopathy, 2 of atrial fibrillation and severe hypertension and one case of coronary artery disease.

Outcome

Overall, 319 patients were evaluable for response (R-CHOP arm, n= 159; R-CHOP+RT, n= 160). With a median follow-up of 64 months (range: 24-132), in an intent to treat analysis, five year EFS was not statistically significantly different between the two arms, with $89\% \pm 2.9$ in the R-CHOP arm vs $92\% \pm 2.4$ in the R-CHOP+RT arm (HR 0.61 [95%CI 0.3 to 1.2], $p=0.18$) (Figure 2a). OS did not differ between the two arms, with five-year estimates of $92\pm 2.5\%$ for patients assigned to R-CHOP alone, and $96\pm 1.7\%$ (HR 0.62 [95% CI:0.3-1.5], $p=0.28$) for those assigned to R-CHOP+RT (figure 2b). OS for patients in CR after the fourth cycle of R-CHOP was similar in both arms (figure 3). After the fourth cycle of R-CHOP, OS and EFS were not statistically different either between patients who reached CR (n=281) and those considered in PR (n=38) (Supplemental figure 3a).

Pooling both arms, EFS was significantly affected by mIPI (HR 2.8, [95%CI 0.6-14.1]; $p=0.04$)

comparing very good prognosis patients (mIPI 0/1) to those with mIPI=2 (Supplemental figure 3b).

Neither the cell of origin pattern, nor the presence or not of extra-nodal sites did not impact EFS or

OS. Similarly, there was no difference in outcome between Ann Arbor stage I and II patients without any other risk factor.

There were 21 relapses, 13 in the R-CHOP alone arm (5 at the initial site), and 10 in the R-CHOP+RT arm (never in the irradiated field). Considering the CR patients after the fourth cycle of R-CHOP, 10 patients relapsed in each arm. The median time to relapse for the whole group was 21 months (range: 4-93) without any difference between the two arms. (Figure 4).

There were 21 deaths, 12 in the R-CHOP alone arm, and 9 in the R-CHOP+RT arm. Deaths were due to progressive disease (n=11), secondary malignancies (n=3: 1 case of acute myeloid leukemia, colon cancer and pancreatic adenocarcinoma, respectively), accident (n=2), stroke (n=1), late onset infection (n=1), unknown (n=3).

The median relative dose-intensity of cytotoxic drugs (adriamycin and cyclophosphamide) was 97% (97–98) of the planned schedule. Intervals between each cycle of R-CHOP were respected from cycle 1 to cycle 4 and cycle 5 to cycle 6 with a median of 14 days. The 4 days median of delay between cycle 4 and cycle 5 was mainly due to the time needed to check response assessment by PET. The median time between the last R-CHOP course and day 1 of radiotherapy was 36 days (10-132).

During R-CHOP administration, hematological toxicity was rare with 66 episodes of febrile neutropenia occurring in 50 patients during chemotherapy. There were 4 severe infections and one death due to septic shock. Red blood-cell transfusions were needed for 18 patients (6%). There was no grade 4 thrombocytopenia. After radiotherapy, two patients presented with grade 3 mucositis and jaw radionecrosis was observed in one case. Severe and moderate cardiac toxicity were observed in 5 and 8 cases respectively, regardless the arm of treatment.

DISCUSSION

This prospective randomized trial, which enrolled 334 patients with low-tumor burden limited-stage DLBCL, compared R-CHOP alone with R-CHOP followed by IF-RT. This first randomized study in the rituximab era reports definitive results showing a similar outcome with these two options in this specific population of patients. With more than 5-years follow-up, EFS and OS are indeed identical between the two arms.

It must be stressed that only patients with non-bulky tumor (<7cm) were selected. In fact, even in 2017, the definition of bulky disease remains arbitrary and varies between 5 and 10 cm depending on the studies and the cooperative groups.^{14, 19-20} Even if tumor-size is not integrated in the IPI scoring system, several studies have identified it as a prognostic factor, patients with a high tumor mass (usually defined as above 5 cm) having a worse clinical outcome than those with low tumor-burden.^{6, 14, 19-20} Whether or not RT should be limited to high tumor-burden localized DLBCL in the rituximab era remains questionable. In the UNFOLDER trial (Unfavorable Low-Risk Patients Treated With Densification of R-Chemo Regimens), patients with bulky tumor were randomly assigned to R-CHOP with or without RT, yet interim analysis showed a higher incidence of relapse in patients without RT and the R-CHOP alone arm was prematurely closed.²⁶ The impact of tumor burden was confirmed in the MINT trial but not in the retrospective analysis of the RICOVER trial.^{20,25} Furthermore, in the LNH 03-2B GELA/LYSA trial, the high dose-CHOP alone regimen (ACVBP) was superior to CHOP+RT according to low age-adjusted IPI.⁶ Even if RT is supposed to induce better local tumor control, it does not prevent systemic relapse.

PET has become an essential tool for both staging and response-assessment in DLBCL. More than 20% stage I or II disease patients evaluated using CT-scan are upstaged upon PET assessment.²⁶ CT-scan evaluation alone thus leads to underestimate RT fields. In this trial, we included only patients with stage I or II disease based on baseline PET, a position not adopted in previously published studies.^{2, 10, 14, 20} Of note, this trial was designed before the development of more accurate response criteria²⁸ and

PET analysis relied on visual analysis. This, however, did not impact response assessment since nearly 90% of patients remained or became PET negative after 4 R-CHOP. The majority of patients (281/319;88%) reached complete remission after 4 R-CHOP cycles, which is 10% more than what is observed in more advanced DLBCL patients treated with rituximab-combined chemotherapy.²⁹ Whether or not these patients should receive 4 or 6 cycles of R-CHOP is currently questioned in the ongoing 09-1B ongoing LYSA trial (NCI: NCT01285765).³⁰

Thirty eight patients (12%) had partial response after 4 R-CHOP based on PET visual analysis.

Persistent PET positivity may be related to disease persistence or inflammatory process. Biopsy was not recommended in this trial. Of these 38 patients, 28 finally achieved CR after receiving additional chemotherapy and/or radiotherapy, meaning that PET-positive signals observed after cycle 4 were mainly related to residual lymphoma. Interestingly, the outcome of these PR patients did not differ from those reaching CR after 4 R-CHOP, as already reported¹⁶

In this selected group of limited-stage DLBCL, the relapse rate was very low, with a median time of 21 months and indeed no patient presented onsite relapse in the RT arm. In the literature, relapse rates after RT vary from 0 to 34%.^{1,5-7,14} Our study is thus the second to report the absence of local relapse after RT. This may be explained by the low tumor burden of the patients, which allowed RT to induce an optimal tumor control locally, hence the low number of overall relapses. Late relapse occurred very rarely as only 4 patients displayed disease recurrence after 5 years. This confirms a previously reported series of our group, in which 213 patients with localized DLBCL were treated with 3 cycles of high dose CHOP and radiotherapy, and where only 9 patients relapsed after five years, with a median follow-up of 88 months.³¹ Of note, this was not observed in the long-term analysis of the SWOG S8736 study which compared 8 CHOP alone to 3 CHOP followed by RT.⁹

However, the selection of patients widely differed from that of our study: initial staging and response assessment were not based on PET imaging, patients with bulky disease were included, histology did

not match with accurate classification and, importantly, treatment did not include rituximab, making the conclusions more hazardous. In our trial, with an EFS higher than 90% at 5 years for CR patients, we confirm the excellent outcome of low-burden DLBCL patients who do not present early relapse and reach a survival nearly equivalent to that of the general population.³²⁻³³

This trial was designed at a time when shortening the interval between R-CHOP cycles was questioned (i.e. 2 or 3 weeks). Although we did not observe increased toxicity with a two-week interval schedule (R-CHOP 14), a three-week delivery (R-CHOP 21) appears now to be the best option, based on recent randomized studies showing similar results between these two regimens³⁴⁻³⁵ and could be proposed to patients meeting our trial inclusion criteria.

In conclusion, this trial prompts to recommend that patients with non-bulky limited stage DLBCL who reach complete remission based on PET evaluation after 4 or 6 R-CHOP cycles should be spared additional RT, thus avoiding radiation-related toxicity. As already proposed¹⁶, PET could help to deliver RT to the minority of patients with residual PET-positive tumors.

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Authorship Contributions:

TL, PS, GC, and PC designed the study. TL, GD, PS, EG, GC, KB, RG, JC, AB, K LD, MB, MP M, SL G, FJ, GP, HM, ED, RH, KI L, J PM, OT, BB, AD, JP V, FT, PC were responsible for patient recruitment, data collection. VC and VS performed pathological central review. JP V contributed to PET review. BB and MCB performed statistical analysis. TL and MCB performed the final analysis and wrote the paper. All authors approved the final version of the manuscript and the submission

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References

- 1) Shenkier TN, Voss N, Fairey R et al: Brief Chemotherapy and Involved-Region Irradiation for Limited-Stage Diffuse Large-Cell Lymphoma: An 18-Year Experience From the British Columbia Cancer Agency. *Journal of Clinical Oncology* 2002; 20(1):197-204
- 2) Persky DO, Unger JM, Spier CM et al. Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014. *Journal of Clinical Oncology* 2008; 26(14):2258-2263.
- 3) Miller TP. The Limits of Limited Stage Lymphoma. *Journal of Clinical Oncology* 2004; 22(15):2982-2984
- 4) Zelenetz AD, Abramson JS, Advani RH, et al: NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's lymphomas. *Journal National Comprehensive Cancer Network* 2010; 8(3):288-334
- 5) Bonnet C, Fillet G, Mounier N, et al: CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: A study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology* 2007; 25(7):787-792
- 6) Reyes F, Lepage E, Ganem G, et al: ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *New England Journal of Medicine* 2005;352(12):1197-1205
- 7) Horning SJ, Weller E, Kim K, et al: Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 484 *Journal of Clinical Oncology* 2004; 22(15):3032-3038
- 8) Miller TP, Dahlberg S, Cassady JR, et al: Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *New England Journal of Medicine* 1998; 339(1):21-26
- 9) Stephens DM, Li H, LeBlanc ML et al: Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736. *Journal of Clinical Oncology* 2016; 34(25): 2997-3004
- 10) Yahalom J. Radiation Therapy after R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains. *Journal of Clinical Oncology* 2010; 28(27):4105-4107
- 11) Vargo JA, Gill BS, Balasubramani GK, et al: Treatment selection and survival outcomes in early-stage diffuse large B-cell lymphoma: Do we still need consolidative radiotherapy? *Journal of Clinical Oncology* 2015;33(32):3710-3717
- 12) Longo DL: Combined-modality therapy for early-stage diffuse large B-cell lymphoma: Knowing when to quit. *Journal of Clinical Oncology* 2015;33(32):3684-3685
- 13) Persky DP and Miller TP. Localized large cell lymphoma: is there any need for radiation therapy? *Current Opinion in Oncology* 2009, 21(5):401-406
- 14) Phan J, Mazloom A, Medeiros LJ, et al: Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *Journal of Clinical Oncology* 2010; 28(27):4170-4176
- 15) Ng AK, Dabaja BS, Hoppe RT, Illidge T, Yahalom J. Re-Examining the Role of Radiation Therapy for Diffuse Large B-Cell Lymphoma in the Modern Era. *Journal of Clinical Oncology* 2016; 34(13):1443-1447.
- 16) Sehn LH: Chemotherapy alone for localized diffuse large B-cell lymphoma. *Cancer Journal* 2012; 18(5):421-426
- 17) Sehn LH and Gascoyne RD: Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. *Blood* 2015; 125(1):22-32
- 18) Jaffe ES, Harris NL, Stein H, et al: *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. 2001, Lyon, France: IARC Press

- 19) Nieder C, Licht T, Andratschke N, et al: Influence of differing radiotherapy strategies on treatment results in diffuse large-cell lymphoma: a review. *Cancer Treat Rev* 2003; 29(1): 11–19.
- 20) Pfreundschuh M, Kuhnt E, Trümper L, et al: CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncology* 2011; 12(11):1013-1022
- 21) Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. In: Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H, eds. World Health Organization Classification of Tumours. 2008. Lyon, France: IARC
- 22) Spaepen K, Stroobants S, Verhoef G, et al: Positron emission tomography with [(18)F]FDG for therapy response monitoring in lymphoma patients. *European Journal of Nuclear Medicine and Molecular Imaging*. 2003; 30 Suppl 1:S97-105.
- 23) Roberts RA, Rimsza LM, Staudt L, et al: Gene expression differences between low and high stage diffuse large B cell lymphoma (DLBCL). *Blood* 2006;108 (abstr 809)
- 24) A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *New England Journal of Medicine* 1993;329(14):987-994
- 25) Held G, Murawski N, Ziepert M, et al: Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *Journal of Clinical Oncology* 2014;32(11):1112-1118
- 26) Cheson BD. Role of functional imaging in the management of lymphoma. *J Clin Oncol*. 2011 May 10;29(14):1844-54.
- 27) German High-Grade Non-Hodgkin's Lymphoma Study Group: Rituximab and combination chemotherapy with or without radiation therapy in treating patients with B-cell non-Hodgkin's lymphoma. <https://clinicaltrials.gov/show/NCT00278408>
- 28) Cheson BD. Role of functional imaging in the management of lymphoma. *Journal of Clinical Oncology* 2011; 29(14):1844-1854
- 29) Cheson BD, Fisher RI, Barrington SF. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *Journal of Clinical Oncology* 2014; 32(27):3059-3067
- 30) Cortelazzo S, Tarella C, Gianni AM et al : Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients with Diffuse Large B-Cell Lymphomas. *Journal of Clinical Oncology* 2016; 34(33):4015-4022
- 31) Study Evaluating the Non-inferiority of a Treatment Adapted to the Early Response Evaluated With 18F-FDG PET Compared to a Standard Treatment, for Patients Aged From 18 to 80 Years With Low Risk (aa IPI = 0) Diffuse Large B-cells Non-Hodgkin's Lymphoma CD 20+. Lysa trial. <http://clinicaltrials.gov/ct2/show/NCT01285765>
- 32) Bernard M, Cartron G, Rachieru P et al: Long-term outcome of localized high-grade non-Hodgkin's lymphoma treated with high dose CHOP regimen and involved field radiotherapy: results of a GOELAMS study. *Haematologica* 2005; 90(6):802-809
- 33) Maurer MJ, Ghesquières H, Jais JP, et al: Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *Journal of Clinical Oncology* 2014; 32(10):1066-1073
- 34) Jakobsen LH, Bogsted M, de Nully Brown P et al. Minimal Loss of Lifetime for Patients With Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months After Treatment: A Danish Population-Based Study. *Journal of Clinical Oncology* 2017; 35(7):778-784
- 35) Cunningham D, Hawkes EA, Jack A et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin

lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet* 2013; 381(9880):1817-26.

- 36) Delarue R, Tilly H, Mounier N et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncology* 2014;14(6):525-533

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Table 1: Clinical characteristics of the 327 evaluable patients.

| | R-CHOP | R-CHOP + RT |
|---|--------------------|--------------------|
| Number assigned | 163 | 164 |
| M/F ratio | 94/69 | 102/62 |
| Age > 60 yr / < 60yr n (%) | 55 (34%)/108 (66%) | 62 (38%)/102 (62%) |
| Modified IPI (Miller) n (%) | | |
| 0 | 89 (55%) | 94 (57%) |
| 1 | 65 (40%) | 59 (36%) |
| 2 | 7 (4%) | 9 (6%) |
| 3 | 2 | 1 |
| LDH <ULN n (%) | 131 (80%) | 138 (84%) |
| ECOG n= | | |
| 0-1 | 157 | 161 |
| ≥2 | 2 | 3 |
| Extra nodal sites n (%) | 63 (40%) | 66 (42%) |
| Anatomical site | | |
| Cervical | 85 | 85 |
| Axillary | 18 | 12 |
| Mediastinal | 9 | 12 |
| Inguinal-femoral | 17 | 14 |
| Pathology centrally reviewed (263/80%) | | |
| Misdiagnosis | 2 | 2 |
| COO (62% analyzed) | | |
| GC | 50 | 58 |
| Non GC | 27 | 26 |
| Undetermined | 15 | 17 |

RT: radiotherapy; IPI: International Prognostic Index; LDH: Lactate DeHydrogenase; ULN: Upper Laboratory Normal value; ECOG: Eastern Cooperative Oncology Group; COO: Cell Of Origin; GC: Germinal Center.

Table 2: results according to the treatment arm in the 319 assessable patients

| | R-CHOP n=159 | R-CHOP + RT n=160 |
|-------------------------|---------------------|--------------------------|
| After C4 | | |
| CR n (%) | 137 (86%) | 144 (90%) |
| PR (PET+) n (%) | 22 (14%) | 16 (10%) |
| End of Treatment | | |
| CR n(%) | 150 (94%) | 157 (98%) |
| PR n= | 8 | 2 |
| Progression n= | 0 | 1 |
| Relapse n(%) | 13 (8%) | 10 (6%) |
| Secondary malignancy n= | 2 | 2 |
| Deaths n(%) | 12 (8%) | 9 (6%) |

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Figure Legends

Figure 1: Consort Diagram.

Figure 2a: Kaplan-Meier Analysis of Event-free survival calculated from time of inclusion.

Solid line R-CHOP, dotted line R-CHOP+RT

Figure 2b: Kaplan-Meier Analysis of Overall Survival calculated from time of inclusion.

Solid line R-CHOP, dotted line R-CHOP+RT

Figure 3: Kaplan-Meier Analysis of overall survival for patients in complete remission at C4 according to randomization. Solid line: R-CHOP, dotted line R-CHOP+RT

Figure 4: Incidence of relapse according to treatment arm.

Solid line: R-CHOP, dotted line R-CHOP+RT.

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Figure 1: Consort Diagram

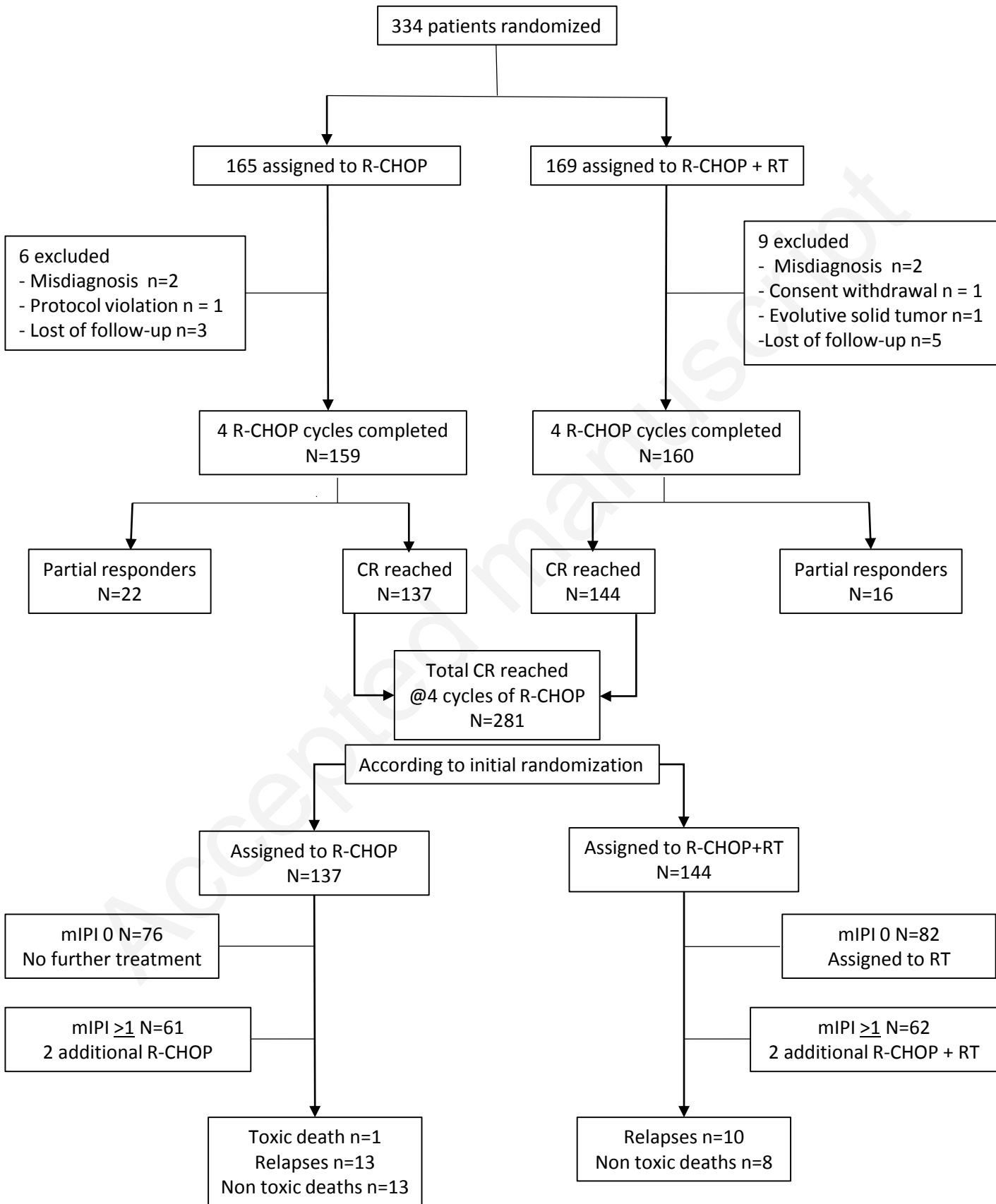


Figure 2a: Kaplan-Meier Analysis of Event-free survival calculated from time of inclusion.

Solid line R-CHOP, dotted line R-CHOP+RT

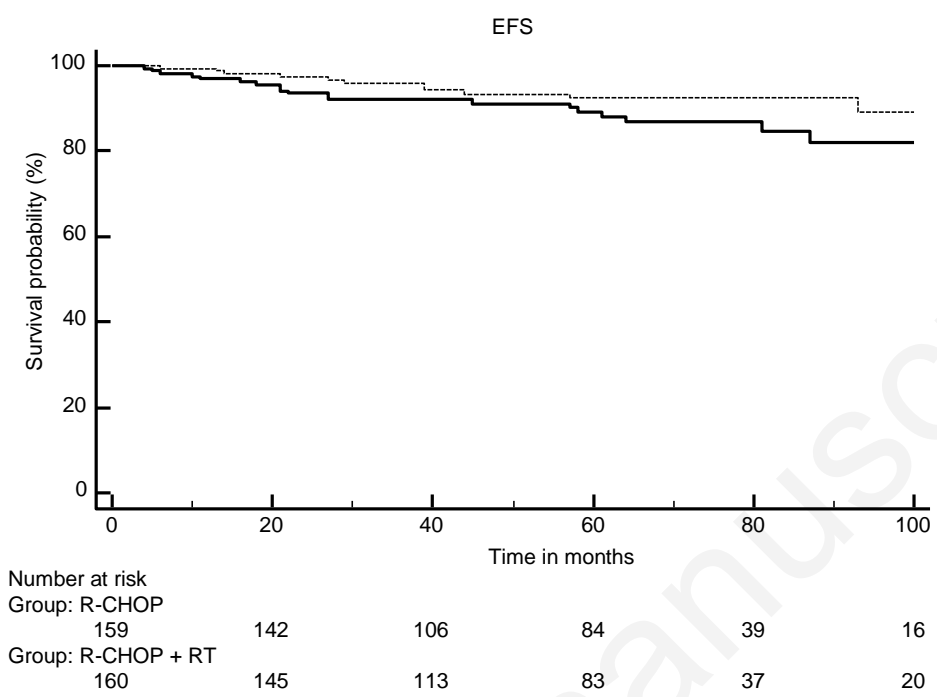


Figure 2b: Kaplan-Meier Analysis of Overall Survival calculated from time of inclusion.

Solid line R-CHOP, dotted line R-CHOP+RT

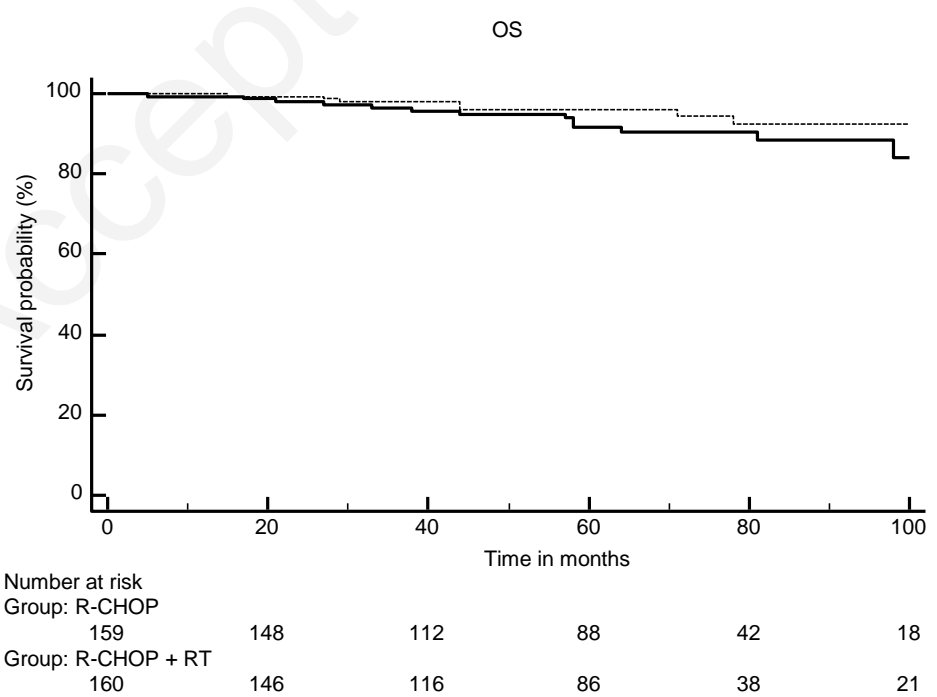


Figure 3: Kaplan-Meier Analysis of overall survival for patients in complete remission at C4 according to randomization. Solid line: R-CHOP, dotted line R-CHOP+RT

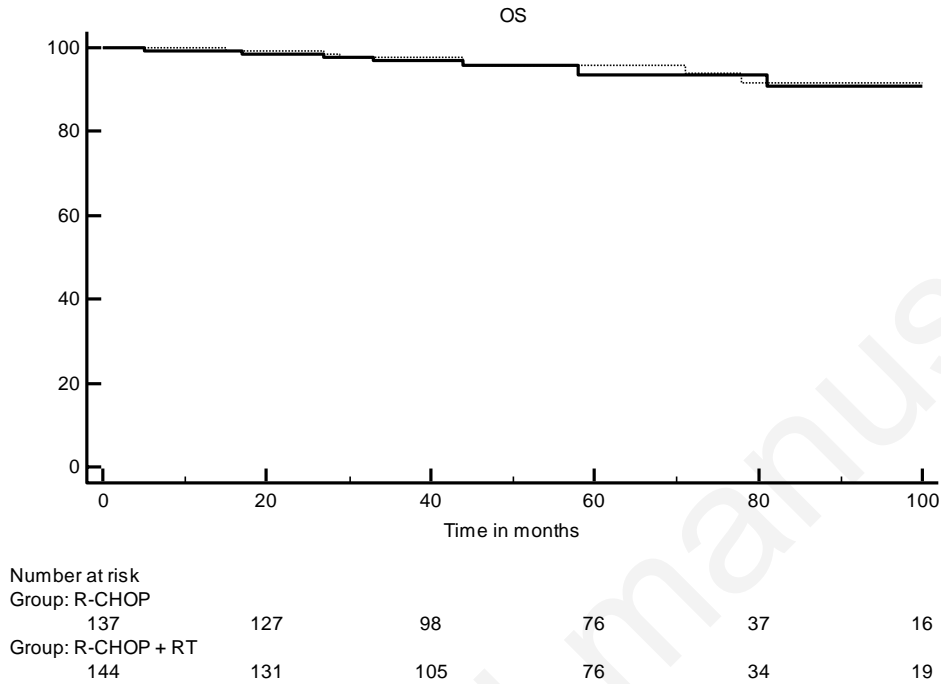


Figure 4: Incidence of relapse according to treatment arm.

Solid line: R-CHOP, dotted line R-CHOP+RT.

