Published in final edited form as:

Br J Haematol. 2015 December ; 171(5): 776–783. doi:10.1111/bjh.13766.

Excellent Outcomes and Lack of Prognostic Impact of Cell of Origin for Localized Diffuse Large B-cell Lymphoma in the Rituximab Era

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Summary

Therapeutic options for limited-stage diffuse large B cell lymphoma (DLBCL) include short- or full-course R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) +/- radiotherapy. The optimal treatment remains unclear. The prognostic value of cell-of-origin (COO) in early stage DLBCL is unknown. Patients with limited-stage DLBCL (stage I or stage II, non-bulky) treated with R-CHOP +/- involved field radiotherapy (IFRT) from 1999 – 2012 were included. COO by the Hans algorithm was analysed in a subset of patients. Of 261 patients, 30% were stage I (N=82), 37% Stage IE (N=96), <1% stage IXEE (N=1), 18% stage II (N=46) and 14% Stage IIE (N=37). The stage-modified IPI stratified patients into prognostically relevant groups. There was no significant difference in progression-free survival (PFS) or overall survival (OS) for patients in the germinal centre B-cell-like (GCB; n=65) and non-GCB cohorts (n=22). Seventeen patients received R-CHOP x 3-4 cycles (Arm A), 147 received R-CHOP x 3-4 cycles + IFRT (Arm B), 48 received R-CHOP x6 cycles (Arm C), and 50 received R-CHOP x6 cycles + IFRT (Arm D). The outcomes were excellent, with 5-year PFS of 82% and 5-year OS of 93%, and were similar across the 4 treatment groups. In the rituximab era, outcomes for limited-stage DLBCL, regardless of treatment approach, were excellent. Baseline COO was not a significant prognostic factor in patients treated with short-course R-CHOP + IFRT.

Keywords

diffuse large B-cell lymphoma; chemotherapy; radiotherapy; outcomes; cell-of-origin

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Author Contributions: AK designed the study, performed the research, analysed and interpreted the data, and drafted the manuscript. MAL also designed the study, performed the research, as well as analysed and interpreted the data. ZZ analysed the data and provided biostatistics expertise. JCM also performed the research and analysed the data. ADZ contributed to the analysis and interpretation of the data and was the main editor of the manuscript. All authors read, critically revised and approved the final manuscript.

Conflicts of Interest: AK, MAL, ZZ, JCM, CHM, and ADZ have no conflicts of interest to disclose.

Introduction

Approximately 25% of patients with diffuse large B cell lymphoma (DLBCL) present as localized early-stage disease, generally defined as stage I and non-bulky stage II disease. (Persky and Miller, 2009) Well-delineated selection criteria do not exist to choose between short-course immunochemotherapy or extended-course immunochemotherapy with or without involved field radiotherapy (IFRT) in patients with localized DLBCL. The role of radiotherapy remains controversial and it is unclear which patients are the best candidates for combined modality therapy.

Four randomized trials have compared systemic chemotherapy versus combined modality therapy in localized DLBCL prior to the introduction of rituximab for the treatment of DLBCL. These studies, the Southwest Oncology Group (SWOG) 8736, Groupe d'Etude des Lymphomes de l'Adulte (GELA) Lymphome Non Hodgkinien (LNH)-93-1, Eastern Cooperative Oncology Group (ECOG) 1484 and GELA LNH 93-4, did not clarify the optimal treatment approach for localized DLBCL. (Miller et al., 1998) (Bonnet et al., 2007) (Horning et al., 2004) (Reyes et al., 2005) (Miller et al., 2001) After the introduction of rituximab, the phase II SWOG 0014 study demonstrated the efficacy of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) x3 cycles followed by IFRT in patients with at least 1 adverse stage-modified International Prognostic Index (IPI) risk factor (non-bulky stage II disease, age >60 years, World Health Organization (WHO) performance status of 2 or elevated serum lactate dehydrogenase); however, this did not address the optimal treatment approach. (Persky et al., 2008) In the rituximab era, the preliminary results of the first prospective randomized study comparing R-CHOP with or without radiotherapy in non-bulky limited-stage DLBCL were recently reported at the American Society of Hematology (ASH) 2014 conference (Lamy et al., 2014). This study was risk-adapted based on a stage-modified IPI and interim positron emission tomography (PET) after 4 cycles and found that, overall, combined modality therapy was not significantly superior to R-CHOP alone in patients achieving early PET negativity. (Lamy et al., 2014) Several retrospective analyses have reported conflicting results of the comparative effectiveness of short-course immunochemotherapy or extended-course immunochemotherapy with or without IFRT in patients treated with R-CHOP. (Phan et al., 2010) (Terada et al., 2012) (Odejide et al., 2015) (Tomita et al., 2013)

There is also a paucity of data regarding the prognostic significance of the cell-of-origin (COO), the germinal centre B-cell-like (GCB) subtype and non-germinal centre B-cell-like (non-GCB) subtype, in early stage DLBCL. (Alizadeh et al., 2000) (Rosenwald et al., 2002) Among all patients with DLBCL, the non-GCB subtype has been correlated with inferior overall survival (OS) when COO is determined by gene expression profiling (GEP) or the Hans immunochemistry-based algorithm. (Hans et al., 2004) The difference in outcomes by COO specifically in patients with localized DLBCL has not been reported.

We performed a retrospective analysis of localized DLBCL patients treated at the Memorial Sloan Kettering Cancer Center and compared outcomes associated with different treatment programmes including 3-4 cycles of R-CHOP +/- IFRT and 6 cycles of R-CHOP +/- IFRT. We also examined the prognostic significance of COO, GCB and non-GCB phenotypes, as

determined by the Hans immunohistochemistry-based algorithm, in localized DLBCL.(Hans et al., 2004)

Patients and Methods

Patients

In this single-centre retrospective study, all patients with newly diagnosed limited-stage DLBCL treated at Memorial Sloan-Kettering Cancer Center (MSKCC) with R-CHOP chemotherapy with or without IFRT from 1999 – 2012 were eligible for inclusion in this analysis. All pathology was reviewed at MKSCC and confirmed to be *de novo* DLBCL or follicular lymphoma grade 3B per WHO classification of lymphoid malignancies.(Swerdlow et al., 2008) Patients with primary mediastinal large B-cell lymphoma were excluded. Limited-stage DLBCL was defined as patients with stage I or non-bulky stage II disease by Ann Arbor classification (Miller *et al* 1998). Bulky disease was defined as any mass exceeding 10 cm in maximal diameter or a mediastinal mass with maximum width equal or greater than one-third of the internal transverse diameter of the thorax on posteroanterior chest X-ray. The Hans immunohistochemistry (IHC) algorithm was used to classify patients as either GCB or non-GCB.(Hans et al., 2004) This retrospective study was conducted on a waiver of authorization approved by the institutional review board at MSKCC.

Statistical Analysis

Survival analyses were performed using the Kaplan–Meier method in SPSS 21 (IBM corp., Armonk, NY) and version 2.11.0 of R statistical software (R Development Core Team, 2015). Association of clinical and sociodemographic factors with treatment regimen and outcome were evaluated with Chi-Square and Fisher's exact tests. Progression-free survival (PFS) was defined as the time from date of diagnosis until progression of disease, relapse, or death; disease-free survival (DFS) was defined as a time from date of diagnosis until progression of disease or relapse; and OS was defined as the time from date of diagnosis until death from any cause. Log-rank tests were used to compare differences in survival. A *P* value of 0.05 or less was considered statistically significant in this study.

To control for potential confounding factors associated with different treatment regimens, a propensity score analysis based on the Cox proportional hazards model was performed. A propensity score reflects the probability that a patient will receive the therapy conditional on other observed covariates; by assigning propensity score weights to each patient and incorporating these weights into model construction, the relationship between treatment and the outcome is thus adjusted for other covariates (potential confounders) through the propensity score.(Rosenbaum and Rubin, 1984)

Results

Patient Characteristics

A total of 261 patients with newly diagnosed, limited-stage DLBCL were included in the analysis. The median age was 58 years (range 18-85) and there was a slight female predominance (55%). By Ann Arbor stage, 30% of patients were stage I (n=82), 37% Stage

IE (n=96), <1% stage IXEE (n=1), 18% stage II (n=46) and 14% Stage IIE (n=36). There was only one patient with disease bulk (presence of mass > 10 cm). The stage-modified IPPI (SM-IPI, including the factors stage II [vs. I], age >60 years, elevated lactate dehydrogenase (LDH) and ECOG performance status 2) demonstrated SM-IPI risk score distribution of 25% risk score 0, 43% risk score 1, 21% risk score 2 and 11% risk score 3. Four treatment programmes were administered; 16 patients received R-CHOP x3-4 cycles (Arm A), 148 received R-CHOP x3-4 cycles + IFRT (Arm B), 48 received R-CHOP x6 cycles (Arm C), and 49 received R-CHOP x6 cycles +IFRT (Arm D). Table I compares patient characteristics across the four identified treatment groups. Factors that were significantly different across the four treatment groups included stage, B-symptoms, presence of extranodal disease, poor performance status and SMIPI (Table I).

Treatment choice appeared to be driven by the patient's clinical presentation at time of diagnosis. The clinical and demographic features associated with receipt of treatment B versus C (treatment arms analogous to the historical SWOG 8736 study of full-course chemotherapy versus short-course combined modality therapy) are described. Patients with stage II vs. I ($p<0.001$), B-symptoms ($p<0.001$), elevated LDH ($p=0.041$) and poor performance status ($p=0.013$) were significantly more likely to receive R-CHOP x 6 cycles versus R-CHOP x 3-4 cycles + IFRT. Therefore, patients with more extensive disease, systemic symptoms related to lymphoma and elevated LDH were significantly more likely to receive full-course chemotherapy.

To define factors that contributed to selection of the less commonly applied treatment algorithms Arms A and D (short-course immunochemotherapy and full-course immunochemotherapy followed by IFRT, respectively), we performed a systematic chart review to gain insight into physician rationale for treatment selection. Of the 16 patients treated with 3-4 cycles of R-CHOP alone, 75% of patients had either fully resected disease prior to initiation of chemotherapy (n=6) or negative interim PET imaging after 3 cycles of chemotherapy (n=6), following the British Columbia Cancer Agency PET-based treatment algorithm.(Sehn et al., 2011)(Sehn, 2012) None of the patients treated with 3-4 cycles of R-CHOP alone had a high-risk SM-IPI (i.e. 3-4 risk factors). Thirty-nine of the 49 patients (80%) treated with 6 cycles of R-CHOP followed by IFRT had extranodal site involvement . The most common high-risk sites included involvement of testis in 24% (n=12), orbit/nasal/sinus region in 14% (n=7), bone in 12% (n=6) and thyroid in 10% (n=5). Additionally, full-course combined modality therapy was administered in seven patients to address the presence of disease bulk per physician (four of these seven patients also had extranodal involvement). One patient with stage IXEE disease had disease bulk per the study definition (>10 cm); however, the remaining six patients did not technically meet the criteria for bulk per our study, but had masses measuring between 7.6 and 9 cm.

Outcomes

The median follow up for surviving patients in this cohort was 4.7 years. The study outcomes for the entire cohort were excellent, with 5-year PFS and OS of 82% and 93.2%, respectively. To date, a total of 30 patients have progressed or died. Of the total 19 deaths, 7 were attributable to progressive lymphoma. Relapse of DLBCL was documented in 17

patients. Failure occurred outside of radiation fields in all patients who initially received consolidative radiotherapy (n=10). The outcomes were similar for the four treatment groups (Table II). There were no differences in outcomes between treatment arms among elderly patients aged either 70 years (n=65) or 60 years (n=125).

Clinical factors Associated with Outcome

In univariate analyses of all patients, the factors associated with inferior PFS were age > 60 years (p=0.041), elevated LDH (p=0.014) and stage II disease (p=0.014) (Table III). Interim PET imaging after 3-4 cycles (interpreted with International Harmonization Project criteria) was available in 197 patients and the majority (78%) achieved a negative interim PET scan (Juweid *et al* 2007). Positive interim PET imaging was not associated with inferior PFS, p=0.44. The stage-modified IPI stratified patients into prognostically relevant groups (Figure 1). The 5-year PFS for patients with 0, 1, 2 and 3 risk factors was 95.3%, 87.7%, 83.4% and 61.9%, respectively. The 5-year OS for patients with 0, 1, 2 and 3 risk factors was 100%, 95.2%, 85.8% and 74.2 %, respectively. In the rituximab era, the poorest outcomes were observed in patients with SM-IPI=3 (n=21).

Cell of Origin and Outcome

A total of 87 patients treated homogeneously with 3-4 cycles of R-CHOP followed by IFRT had IHC data extracted from pathology reports to determine COO by the Hans algorithm. A GCB phenotype was seen in the majority of patients (65 of 87, 75%). The SM-IPI was not significantly different between the GCB and non-GCB cohorts. At 5 years, the PFS and OS for the GCB cohort was 88% and 97%, respectively, and for the non-GCB cohort 100% for both. There was no significant difference in PFS or OS for patients in the GCB and non-GCB cohorts (Figure 2).

Propensity Score Analysis

Propensity score analysis was performed to compare treatment arms B versus C (3-4 cycles R-CHOP + IFRT versus 6 cycles R-CHOP), the most widely accepted standard treatments for localized DLBCL. The variables significantly associated with treatment choice and included in the propensity score analysis as adjusting confounders for therapy received were stage-modified IPI (including stage [II vs. I], age >60 years, elevated LDH and poor performance status), presence of B-symptoms and presence of extranodal involvement. For PFS, a propensity score analysis yielded a non-significant p-value of 0.81 with a HR of 0.88 (95% CI: 0.30, 2.60). For overall survival, a propensity score analysis yielded a non-significant p-value of 0.63 with a HR of 0.73 (95% CI: 0.21-2.62). The propensity score analysis is consistent with no significant difference in PFS or OS when comparing short-course combined modality therapy versus full-course chemotherapy alone after adjusting for known confounding factors.

Discussion

The findings from this study underscore that there is no single optimal treatment approach for localized DLBCL in the rituximab-era. In fact, our analysis suggests that appropriately selected patients can be successfully treated with short or long-course chemoimmunotherapy

with and without radiotherapy with excellent outcome. In this study, there were no significant differences in outcome (PFS and OS) across the four different treatment groups.

To our knowledge, this represents one of the largest published retrospective analyses of outcomes for patients with localized DLBCL treated with R-CHOP +/- IFRT. A retrospective review from M.D. Anderson Cancer Center analysed outcomes for early and advanced stage DLBCL patients treated with R-CHOP chemotherapy with and without radiotherapy.(Phan et al., 2010) This study reported a benefit associated with RT treatment versus chemotherapy alone for the 190 early stage patients included in the analysis; the 5-year OS and PFS were 92% and 82% for the combined modality approach versus 73% and 68% for chemotherapy alone, respectively. A matched pair analysis was performed to control for potential confounders and showed an improvement in OS and PFS with combined modality therapy vs. chemotherapy alone, however, this matched pair analysis was limited by a small sample size and probably wide confidence intervals for hazard ratio estimates (44 matched pairs), selection bias inherent in subset analysis and matching on only three factors (disease bulk [>5 cm], response to therapy [defined as resolution of original tumours] and IPI score). In contrast, other retrospective analyses presented as ASH abstracts reported no significant differences in outcome for 6-8 cycles of R-CHOP chemotherapy alone versus 3-4 cycles of R-CHOP followed by IFRT.(Terada et al., 2012)(Odejide et al., 2015) One of these abstracts was a large retrospective Surveillance, Epidemiology, and End Results Program (SEER) database analysis comparing treatment with 3-4 cycles of R-CHOP plus RT to 6-8 cycles of R-CHOP in 969 elderly (>65 years) patients with DLBCL, and showed no difference in treatment-free survival and OS using propensity-score weighted Cox regression models.(Odejide et al., 2015) Finally, the recently reported prospective, randomized study of R-CHOP with or without chemotherapy (Phase III 02-03 Lymphoma Study Association/ Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang [LYSA/GOELAMS]Trial) also showed no difference in outcomes for chemotherapy alone versus combined modality therapy in patients achieving early PET-negativity.(Lamy et al., 2014) These studies, in conjunction with our data, suggest that both chemotherapy alone and combined modality therapy are effective treatment strategies in early stage DLBCL.

The outcomes reported in this study are similar to outcomes reported in other prospective studies of localized DLBCL patients treated with rituximab. In the phase II SWOG 0014 study of R-CHOP x 3 cycles followed by IFRT, including 60 patients with at least one SM-IPI risk factor, the 4-year PFS and OS was 88 and 92%, respectively, and the current study found a 4-year PFS and OS of 89 and 96%, respectively.(Persky et al., 2008) In the phase III LYSA/GOELMS study the 5-year EFS and OS was 87% and 90% in R-CHOP arm versus 91% and 95% in R-CHOP+RT arm, respectively (Lamy et al., 2014). It is clear that our single-institutional experience demonstrates outcomes for localized DLBCL that are at least equivalent compared to available historical controls.

The SM-IPI was initially described in the landmark SWOG 8736 study in patients treated with CHOP chemotherapy and includes the 4 risk factors: age greater than 60 years, stage II disease, elevated LDH and poor performance status.(Miller et al., 1998) This prognostic tool effectively stratified patients according to survival outcomes with five-year OS of 95% for patients having none of the risk factors, 77% for patients with one or two risk factors and

50% for three or four risk factors ($P=0.01$). Although the IPI for advanced stage DLBCL has been validated in the rituximab era (known as R-IPI), the SM-IPI has not been re-examined in a large cohort of localized DLBCL patients treated with R-CHOP chemotherapy.(Sehn et al., 2007)(Ziepert et al., 2010) After the incorporation of rituximab, overall outcomes have improved for localized DLBCL and the SM-IPI remains predictive, however, now there are two main risk groups identified: patients with 0-2 risk factors have similar outcomes whereas the presence of 3 risk factors distinguishes the poorest risk group with 5-year OS and PFS of 61.9 and 70.7%, respectively.

There is limited data describing gene-expression profiles and cell-of-origin phenotypes specifically in localized DLBCL. The seminal paper describing that non-GCB phenotype was associated with inferior OS included early stage (45%) and advanced stage (55%) patients, however, the data were not analysed separately by stage.(Rosenwald et al., 2002) Multiple subsequent studies describing the clinical importance of COO in DLBCL have not reported COO data among localized DLBCL patients.(Scott et al., 2014)(Monti et al., 2005) In one rare and aggressive subtype of localized extranodal DLBCL, testicular lymphoma, there has been increasing insight about its distinct biology and reports that the majority, 60-96%, of primary testicular lymphoma is ABC-subtype.(Al-Abbadi et al., 2006)(Booman et al., 2006)(Cheah et al., 2014)(Hasselblom et al., 2004)(Li et al., 2010) Our study demonstrates that the majority of localized DLBCL, approximately 75%, is germinal centre phenotype. This is the first study that has correlated COO by the IHC Hans algorithm with outcome and, in contrast to advanced stage DLBCL, COO does not appear to influence outcomes in early stage non-bulky DLBCL treated with combined modality therapy. The conclusion is limited to COO determined by IHC, which has recognized limitation in the determination of COO. It is possible that gene expression approaches (Lym2Cx, Fluidigm, or High Throughput Genomics) would provide an alternative result. In addition, this analysis was limited to a small cohort of patients treated with short-course combined modality therapy and may not be generalizable to all patients with early stage DLBCL.

Patients with localized DLBCL at MSKCC were selected for a specific treatment programme based upon a number of factors, such as: age and comorbidity, clinical presentation including the factors in the SM-IPI, presence of disease bulk, extranodal site involvement, evidence of fully resected disease, interim response assessment and disease biology. In specific clinical scenarios, a particular treatment approach may be indicated, for example, patients with high-risk extranodal site involvement will probably benefit from 6 cycles of R-CHOP followed by IFRT. But in general, the propensity-score weighted survival analysis comparing treatment B vs. C, which demonstrated no difference in PFS or OS for full-course chemotherapy versus short-course combined modality therapy, suggests that these regimens may be equivalent for the large majority of localized DLBCL patients. Although one must be careful to not overinterpret the data from this retrospective series and seek to validate the findings prospectively, a potential rational treatment algorithm based on our data for localized DLBCL is proposed in Figure 3.

There are a number of limitations to this retrospective study. Due to the low number of events in this cohort of patients, there is limited power to detect differences across treatment groups. Predominantly univariate analyses were performed due to a limited number of

events, so there may be confounding effects in absence of multivariate analyses. In addition, the Hans IHC-based algorithm is not a perfect surrogate for the gold standard gene expression profiling-based classification, with a reported sensitivity of 71% in GCB-subtype and 88% in non-GCB-subtype. (Hans et al., 2004) Many relevant prognostic factors, particularly those related to disease biology, such as Ki67 proliferation index or presence of cytogenetic abnormalities (i.e. *MYC* gene rearrangement), were not uniformly captured during the time period of our retrospective study and were not included in analyses. With on-going efforts to elucidate relevant biomarkers and disease biology in early stage DLBCL, these factors will probably become part of risk stratification in localized DLBCL and inform the selection of biologically-based treatments.

In summary, baseline COO does not appear to be a significant prognostic factor in patients treated with short-course combined modality therapy. In the rituximab-era, outcomes for localized DLBCL were excellent across different treatment paradigms.

Acknowledgments

Sources of Funding: Zhigang Zhang's research was partly supported by an NIH Core Grant P30 CA008748.

References

- Al-Abbadi MA, Hattab EM, Tarawneh MS, Amr SS, Orazi A, Ulbright TM. Primary testicular diffuse large B-cell lymphoma belongs to the nongerminal center B-cell-like subgroup: A study of 18 cases. *Modern pathology*. 2006; 19:1521–7. [PubMed: 16998463]
- Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JJ, Yang L, Marti GE, Moore T, Hudson J Jr. Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000; 403:503–11. [PubMed: 10676951]
- Bonnet C, Fillet G, Mounier N, Ganem G, Molina TJ, Thieblemont C, Ferme C, Quesnel B, Martin C, Gisselbrecht C, Tilly H, Reyes F, Groupe D'etude Des Lymphomes de l'Adulte. 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: Official Journal of the American Society of Clinical Oncology*. 2007; 25:787–92. [PubMed: 17228021]
- Booman M, Douwes J, Glas AM, De Jong D, Schuurin E, Kluin PM. Primary testicular diffuse large B-cell lymphomas have activated B-cell-like subtype characteristics. *Journal of Pathology*. 2006; 210:163–71. [PubMed: 16823896]
- Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. *Blood*. 2014; 123:486–93. [PubMed: 24282217]
- Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Muller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, Pan Z, Farinha P, Smith LM, Falini B, Banham AH, Rosenwald A, Staudt LM, Connors JM, Armitage JO, Chan WC. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004; 103:275–82. [PubMed: 14504078]
- Hasselblom S, Ridell B, Wedel H, Norrby K, Sender Baum M, Ekman T. Testicular lymphoma--a retrospective, population-based, clinical and immunohistochemical study. *Acta Oncologica*. 2004; 43:758–65. [PubMed: 15764222]
- Horning SJ, Weller E, Kim K, Earle JD, O'connell MJ, Habermann TM, Glick JH. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2004; 22:3032–8. [PubMed: 15210738]

- Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, Wiseman GA, Kostakoglu L, Scheidhauer K, Buck A, Naumann R, Spaepen K, Hicks RJ, Weber WA, Reske SN, Schwaiger M, Schwartz LH, Zijlstra JM, Siegel BA, Cheson BD, Imaging Subcommittee of International Harmonization Project in Lymphoma. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2007; 25:571–8. [PubMed: 17242397]
- Lamy T, Damaj G, Gyan E, Soubeyran P, Bouabdallah K, Cartron G, Gressin R, Cornillon J, Banos A, Moles M-P, Le Du K, Benchalal M, Costes V, Bene M-C, Delwail V. R-CHOP with or without Radiotherapy in Non-Bulky Limited-Stage Diffuse Large B Cell Lymphoma (DLBCL): Preliminary Results of the Prospective Randomized Phase III 02-03 Trial from the Lysa/Goelams Group. *Blood (ASH Annual Meeting Abstracts)*. 2014; 124
- Li D, Xie P, Mi C. Primary testicular diffuse large B-cell lymphoma shows an activated B-cell-like phenotype. *Pathology Research and Practice*. 2010; 206:611–5.
- Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, Leblanc M, Carlin S, Chase E, Fisher RI. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *New England Journal of Medicine*. 1998; 339:21–6. [PubMed: 9647875]
- Miller TP, Leblanc M, Spier C, Chase E, Fisher RI, the Southwest Oncology Group. CHOP alone compared to CHOP plus radiotherapy for early stage aggressive non-Hodgkin's lymphomas: update of the Southwest Oncology Group (SWOG) randomized trial. *Blood (ASH Annual Meeting Abstracts)*. 2001; 98:724a–725a.
- Monti S, Savage KJ, Kutok JL, Feuerhake F, Kurtin P, Mihm M, Wu B, Pasqualucci L, Neuberg D, Aguiar RC, Dal Cin P, Ladd C, Pinkus GS, Salles G, Harris NL, Dalla-Favera R, Habermann TM, Aster JC, Golub TR, Shipp MA. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood*. 2005; 105:1851–61. [PubMed: 15550490]
- Odejide O, Cronin A, Davidoff AJ, Lacasce AS, Abel GA. Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients. *Leukemia Lymphoma*. 2015; 56:716–24. [PubMed: 24913508]
- Persky DO, Miller TP. Localized large cell lymphoma: is there any need for radiation therapy? *Current Opinion Oncology*. 2009; 21:401–6.
- Persky DO, Unger JM, Spier CM, Stea B, Leblanc M, Mccarty MJ, Rimsza LM, Fisher RI, Miller TP, Southwest Oncology Group. 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: Official Journal of the American Society of Clinical Oncology*. 2008; 26:2258–63. [PubMed: 18413640]
- Phan J, Mazloom A, Medeiros LJ, Zreik TG, Wogan C, Shihadeh F, Rodriguez MA, Fayad L, Fowler N, Reed V, Horace P, Dabaja BS. Benefit of consolidative radiation therapy in patients with diffuse large B-cell lymphoma treated with R-CHOP chemotherapy. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2010; 28:4170–6. [PubMed: 20713859]
- R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; Vienna, Austria: 2015.
- Reyes F, Lepage E, Ganem G, Molina TJ, Brice P, Coiffier B, Morel P, Ferme C, Bosly A, Lederlin P, Laurent G, Tilly H, Groupe D'etude Des Lymphomes de l'Adulte. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. *New England Journal of Medicine*. 2005; 352:1197–205. [PubMed: 15788496]
- Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *Journal of American Statistical Association*. 1984; 79:516–524.
- Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, Gascoyne RD, Muller-Hermelink HK, Smeland EB, Giltmane JM, Hurt EM, Zhao H, Averett L, Yang L, Wilson WH, Jaffe ES, Simon R, Klausner RD, Powell J, Duffey PL, Longo DL, Greiner TC, Weisenburger DD, Sanger WG, Dave BJ, Lynch JC, Vose J, Armitage JO, Montserrat E, Lopez-Guillermo A, Grogan TM, Miller TP, Leblanc M, Ott G, Kvaloy S, Delabie J, Holte H, Krajci P, Stokke T, Staudt LM,

- Lymphoma/Leukemia Molecular Profiling Project. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *New England Journal of Medicine*. 2002; 346:1937–47. [PubMed: 12075054]
- Scott DW, Wright GW, Williams PM, Lih CJ, Walsh W, Jaffe ES, Rosenwald A, Campo E, Chan WC, Connors JM, Smeland EB, Mottok A, Braziel RM, Ott G, Delabie J, Tubbs RR, Cook JR, Weisenburger DD, Greiner TC, Glinnsmann-Gibson BJ, Fu K, Staudt LM, Gascoyne RD, Rimsza LM. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood*. 2014; 123:1214–7. [PubMed: 24398326]
- Sehn LH. Chemotherapy alone for localized diffuse large B-cell lymphoma. *The Cancer Journal*. 2012; 18:421–6. [PubMed: 23006946]
- Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J, Gascoyne RD, Connors JM. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007; 109:1857–61. [PubMed: 17105812]
- Sehn L, Savage KJ, Hoskins P, Klasa R, Shenkier T, Gascoyne RD, Pickles T, Morris J, Wilson D, Benard F, Connors JM. Treatment of limited stage DLBCL can be effectively tailored using a PET-based approach. *Annals of Oncology*. 2011; 22 Abstract 018.
- Swerdlow, SH.; Campo, E.; Harris, NL.; Jaffe, ES.; Pileri, S.; Stein, H.; Thiele, J.; Vardiman, J. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. IARC Press; 2008.
- Terada Y, Take H, Shibayama H, Hashimoto K, Kuwayama M, Fujii N, Azenishi Y, Maeda Y, Yamagami T, Uoshima N, Tsukaguchi M, Semba O, Mitul Y, Ueda S, Soma T, Nakagawa M, Matuda M, Urase F, Kiyoi T, Yoshida H, Sugahara H, Yamashita K, Tominaga N, Kubota T, Arima N, Mori S, Tamaki T, Okamoto T, Anzai N, Akasaka H, Tabata R, Ikeda J, Wada N, Aozasa K, Hino M. Short Cycle of Immunochemotherapy Followed by Radiation Therapy Compared with Prolonged Cycles of Immunochemotherapy for Localized DLBCL: The Osaka Lymphoma Study Group (OLSG) Retrospective Analysis. *Blood (ASH Annual Meeting Abstracts)*. 2012; 120:1628.
- Tomita N, Takasaki H, Miyashita K, Fujisawa S, Ogusa E, Matsuura S, Kishimoto K, Numata A, Fujita A, Ohshima R, Kuwabara H, Hagihara M, Hashimoto C, Takemura S, Koharazawa H, Yamazaki E, Fujimaki K, Taguchi J, Sakai R, Ishigatsubo Y. R-CHOP therapy alone in limited stage diffuse large B-cell lymphoma. *British Journal of Haematology*. 2013; 161:383–8. [PubMed: 23432318]
- Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, Loeffler M. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2010; 28:2373–80. [PubMed: 20385988]

Figure 1. Progression-free survival and overall survival stratified by stage-modified International Prognostic Index (SM-IPI) Risk Factors (RF) pts, patients.

Figure 2. Progression-Free Survival by Cell of Origin
GCB, germinal centre B cell-like; pts, patients

*Factors associated with full course chemotherapy include stage II (vs. I) disease, systemic symptoms related to lymphoma and elevated LDH. This would include patients with high risk SM-IPI: 3-4 risk factors.
†High-risk biology: Elevated proliferative index, *MYC* alteration, complex cytogenetics. COO is probably less applicable.
‡Disease bulk: Unclear cutoff, range 5-10 cm.
§High-risk extranodal site: testis, orbit/nasal/sinus, bone, thyroid, etc.
¶ Per BCCA approach, if PET-3 is negative, can give total of 4 cycles of R-CHOP without RT. This approach is particularly applicable in patients who are elderly or with multiple comorbidities who cannot tolerate prolonged therapy.

Figure 3. Memorial Sloan-Kettering Cancer Center rational treatment algorithm for localized DLBCL based on retrospective analysis
DLBCL, diffuse large B cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; IFRT, involved field radiotherapy; RT, radiotherapy; PET, positron emission tomography; LDH, lactate dehydrogenase; SM-IPI, stage-modified International Prognostic Index; COO, cell of origin; BCCA, British Columbia Cancer Agency.

Table I

Comparison of Patient Characteristics Across Different Treatment Programmes

Characteristic	3-4 R-CHOP N=16	3-4 R-CHOP+RT N=148	6 R-CHOP N=48	6 R-CHOP+RT N=49	P
Age, years (median, range)	61 (25-76)	60 (19-83)	60 (18-84)	56 (20-85)	
60 years	8 (50%)	77 (52%)	25 (52%)	15 (31%)	NS
70 yaesr	6 (38%)	42 (28%)	8 (17%)	7 (14%)	NS
Female	11 (69%)	87 (59%)	25 (52%)	21 (43%)	NS
Ann Arbor Stage					<0.01 *
Stage I	9 (53%)	59 (40%)	10 (21%)	4 (8%)	
Stage IXE	0	0	0	1 (2%)	
Stage IE	6 (35%)	58 (39%)	8 (17%)	24 (49%)	
Stage II	1 (<1%)	17 (11%)	22(46%)	6 (12%)	
Stage IIE		14 (9%)	8 (17%)	14 (29%)	
B-Symptoms	0	2 (1.4%)	9 (23%)	3 (6%)	<0.01
Extranodal Sites	6(38%)	72 (49%)	16 (33%)	39 (80%)	<0.01
Histology					NS
DLBCL	15 (94%)	140 (95%)	45 (94%)	48 (98%)	
FL-Grade 3B	1	8	3	1	
Testicular DLBCL	0	0	1	12	
Sinus DLBCL	0	1	3	7	
LDH >ULN, (N=250)	2 (13%)	30 (21%)	17 (36%)	10 (21%)	NS
Poor Performance Status (ECOG 2), (N=202)	0	1 (1%)	4 (11%)	5 (13%)	0.007
Stage-modified IPI, (N=194)	N=9	N=110	N=36	N=38	0.004
0	2 (22%)	30 (27%)	5 (14%)	11 (30%)	
1	5 (56%)	54 (49%)	9 (25%)	15 (41%)	
2	2 (22%)	20 (18%)	11 (28%)	8 (22%)	
3	0	7 (6%)	11 (28%)	3 (8%)	

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; LDH, lactate dehydrogenase; ULN, upper limit of normal; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostice Index; NS, not significant.

* P value reflects comparison between Stage I vs. II.

Table II

Outcome Analysis (PFS, DFS, and OS) for All Patients Across Treatment Groups

Treatment Group	Survival (%) at 5 years		
	PFS	OS	DFS
3-4 R-CHOP (n=17)	93.8	100	93.8
3-4 R-CHOP+RT (n=147)	89.2	93.5	93.9
6 R-CHOP (n=48)	79.9	84.5	92.9
6 R-CHOP+RT (n=50)	89.8	97.8	89.8

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RT, radiotherapy; PFS, progression-free survival; OS, overall survival; DFS, disease-free survival.

Table III

Demographic and Clinical Characteristics Associated with PFS in Univariate Analysis

Characteristic	5-year PFS	<i>P-value</i>	5-year OS	<i>P-value</i>
Age				
60 years	93.2	0.041	97.8	0.002
> 60 years	82.9		88.3	
Sex				
Female	86.8	0.53	91.7	0.694
Male	90.0		95.1	
Stage				
I	91.6	0.014	95.5	0.107
II	80.5		88.0	
B-symptoms				
No	88.4	0.74	93.7	0.671
Yes	75.0		75.0	
LDH>ULN, (N=250)				
No	90.3	0.014	94.2	0.70
Yes	81.0		88.9	
Poor Performance Status, (N=202)				
No	88.0	0.257	93.9	0.038
Yes	55.6		55.6	
Extranodal sites (Any)				
No	92.6	0.11	95.4	0.20
Yes	84.1		91.3	
Interim PET, (N=198)				
Negative	86.8	0.442	92.2	0.343
Positive	86.9		93.1	

PFS, progression-free survival; OS, overall survival; LDH, lactate dehydrogenase; ULN, upper limit of normal; PET, positron emission tomography.